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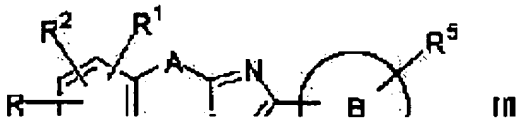
(54) AZOLE COMPOUND AND PHARMACEUTICAL USE THEREOF

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a compound represented by formula [I] having a protein tyrosine phosphatase IB inhibitory activity and useful as a therapeutic agent for diabetes, diabetic complications and hyperlipemia.
SOLUTION: The azole compound is represented by formula [I] {wherein, W is S or O; R is COOR7, X1-A1-COOR7 (R7 is H or an alkyl) or tetrazolyl; R1, R2, R3 and R4 are each H, or the like; A is (CH2)m-X [X is N(R8), C(R9)(R10), CO or CO-



(I)

N(R8)]; B is an aryl or an aromatic heterocyclic group; R5 is H, or the like; R6 is (Y)s1-(A2)s-Z [Y is O, S(O]4, N(R13), N(R14)-CO, N(R14)-SO2, SO2-N(R14), or the like; A2 is an alkylene; and Z is a cycloalkyl, an aryl, an aromatic heterocyclic group, indanyl or piperazinyl]] or its prodrug or a pharmaceutically acceptable salt thereof.

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* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the salt which can be permitted on the azole compound which has protein thyrosin phosphatase 1B (PTP1B;Protein TyrosinePhosphatase 1B) inhibition activity in more detail, or its remedy, and the remedy constituent containing it about a new azole compound.
[0002]
[Description of the Prior Art] Diabetes mellitus is a disease which causes various metabolic errors which made the chronic hyperglycemia condition the cardinal symptom, and shows various symptoms based on hyperglycemia, such as thirst, polyposia, polyuria, and a loss weight. Moreover, if such a hyperglycemia condition continues for a long time, starting various complication, such as myocardial infarction based on a retinopathy, a nephropathy, neuropathy, and arteriosclerosis and cerebral infarction, is also known.
[0003] The I-beam diabetes mellitus which will cause absolute insulin lack by breakage and destruction of beta cells of pancreas if diabetes mellitus divides roughly (IDDM; insulin-dependent diabetes mellitus), The special diabetes mellitus whose symptoms are secondarily shown in connection with II type <2> diabetes mellitus (NIDDM; non-insulin dependent diabetes mellitus) which causes relative insulin lack, abnormalities, other diseases of a gene, etc. by insulin resistance and insulin secretion lowering, the inside of those who were divided into four molds of pregnancy diabetes, and were diagnosed as II type <2> diabetes mellitus at the beginning of the onset -- progress -- gradually -- insulin secretion ability -- falling -- just -- being alike -- it may result in I-beam diabetes mellitus
[0004] By the way, if a living body's saccharometabolism is seen, as opposed to the ingredient used as a living body's energy source or a constituent being incorporated inside of the body intermittently, the brain will consume the glucose without an intermission. In such a situation, the blood sugar level is kept almost constant and the interaction of exchanges, such as a metabolic turnover in the hormone and the organ concerning blood sugar regulation and sugar between organs, makes such blood sugar regulation possible. It is thought that the operation of the insulin which is hormone especially concerning blood sugar regulation is important also in it, and the failure, i.e., insulin resistance, and insulin secretion lowering are participating in diabetes mellitus deeply.
[0005] An insulin is secreted from beta cells of pancreas, and after combining with the insulin receptor in the film front face of a skeletal muscle cell or a fat cell which is the target cell, self-phosphorylation of the thyrosin residue of an intracellular domain is carried out. Then, phosphorylation of the thyrosin residue which is the substrates of an insulin receptor, such as IRS (insulin receptor substrate) and APS (adapter protein containing PH and SH2 domain), is carried out, when an PI3 kinase-Akt path is activated, a glucose transporter is made to shift to up to a cell membrane, incorporation of a glucose takes place, and the sugar concentration in blood falls. On the other hand, the thyrosin phosphatase which performs thyrosin dephosphorization which adjusts the intracellular signaling by this insulin to negative also existed, and that activation is controlled. Thus, although thyrosin phosphorylation is bearing the central role in an insulin operation, if thyrosin phosphorylation considers being decided by

balance of the activity of the thyrosin phosphatase which is the tyrosine kinase and phosphatase which are phosphorylated enzyme, it will be thought that thyrosin phosphatase has played the important modulatory role which participates in insulin signal transfer directly with tyrosine kinase.
[0006] Although current and thyrosin phosphatase form a big gene family and about seventy or more kinds of isozymes are reported, it is thought also in it that protein thyrosin phosphatase 1B (PTP1B;Protein Tyrosine Phosphatase 1B) is phosphatase specific to insulin signal transfer. It is admitted that the gene expression of PTP1B increases by high grape-sugar culture especially. The intracellular localization changes and an insulin receptor and the thyrosin phosphorylation of IRS-1 decrease. guiding insulin resistance (nonpatent literature 1:J.Biol.Chem., 1995, the 270th volume, and p.7724-7730; nonpatent literature 2:J.Biochem. (Tokyo) --) The failure of the translocation of the sugar transporter GLUT4 was carried out by installation of the wild type of the 123rd volume, p.813-820, and PTP1B, and the effectiveness was not accepted by the phosphatase activity deficit mutant in 1998, Furthermore, insulin susceptibility reinforces by the knockout mouse of PTP1B recently. Moreover, since it was reported that it became obesity resistance to a high fat food (nonpatent literature 3:Science, 1999, the 283rd volume, p.1544-1548), it is suggested that this enzyme can become one target of an insulin resistance improvement. It is admitted that the vanadium acid known shows an insulin resistance improvement effect in an animal experiment etc. actually from before as thyrosin phosphatase inhibitor.
[0007] Therefore, such thyrosin phosphatase, especially the drug which controls and/or checks abnormality activation of PTP1B improve insulin susceptibility, insulin resistance, and/or glucose tolerance, and can serve as diabetic medicine new type which returns the intracellular signaling of an insulin to normal. Moreover, the application to various disease remedies, such as obesity and a neurodegenerative disease, is also expectable.
[0008] It continues till recently and various reports are made about the compound aiming at treating diseases, such as diabetes mellitus, by checking protein thyrosin phosphatase in this way.
[0009] For example, patent reference 1: The phosphonic acid derivative which has PTP1B inhibitory action is indicated by the international disclosure/[00th] No. 17211 pamphlet. However, in this official report, the publication of the purport which suggests it is not found as well as disclosure of the compound which has the structure like this invention compound, either.
[0010] Patent reference 2: The aryl acrylic-acid derivative useful as a protein thyrosin phosphatase inhibitor is indicated by the Patent Publication Heisei No. 508919 [11 to] official report (patent reference 3: U.S. Pat. No. 5,770,620 description). However, in this official report, the publication of the purport which suggests it is not found as well as disclosure of the compound which has the structure like this invention compound, either.
[0011] Patent reference 4: The thiazole compound which has protein thyrosin phosphatase inhibitory action is indicated by the international disclosure/[98th] No. 27092 pamphlet (patent reference 5: U.S. Pat. No. 6,080,772 description). However, in this official report, the publication of the purport which suggests it is not found as well as disclosure of the compound which has the structure like this invention compound, either.
[0012] In an international disclosure/[99th] No. 58522 pamphlet, Patent reference 6 : a [2 and 3-naphth B] HETEROARU-4-IRU derivative In an international disclosure/[99th] No. 58511 pamphlet, Patent reference 7 : OKISA / thiazole-aryl-carboxylic-acid derivative On U.S. Pat. No. 6,110,962 descriptions, Patent Reference 8: An international disclosure/[99th] No. 58521 pamphlet and patent reference 9 : the 11-aryl-[benzoB] [2 and 3-naphth D] furan and the 11-aryl-[benzoB] [2 and 3-naphth D] thiophene derivative In an international disclosure/[99th] No. 58518 pamphlet, Patent reference 10 : a biphenyl-oxo--acetic-acid derivative In an international disclosure/[99th] No. 61419 pamphlet, Patent reference 11 : 2, 3, and 5-permutation biphenyl derivative In an international disclosure/[99th] No. 58520 pamphlet, Patent reference 12 : a biphenyl-sulfonyl-aryl-carboxylic-acid derivative In an international disclosure/[99th] No. 61435 pamphlet, Patent reference 13 : Benzothiophene, Benzofuran and indole derivatives on patent reference 14:U.S. Pat. No. 6,103,708 descriptions A furan, Benzofuran and a thiophene derivative on patent reference 15:U.S. Pat. No. 6,110,963 descriptions an aryl-oxo--acetic-acid derivative On U.S. Pat. No. 6,001,867 descriptions, Patent reference 16 : a 1-aryl-dibenzo

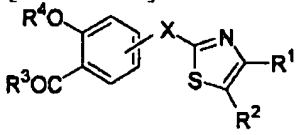
thiophene derivative On U.S. Pat. No. 6,057,316 descriptions, Patent reference 17 : the 4-aryl-1-OKISA-9-thia-cyclo [PENTA B] fluorene derivative Patent reference 18: A benzophenone derivative is indicated by them noting that it has protein thyrosin phosphatase inhibitory action on U.S. Pat. No. 6,063,815 descriptions, respectively. However, in these official reports, the publication of the purport which suggests it is not found as well as disclosure of the compound which has the structure like this invention compound, either.

[0013] Moreover, the following are reported as a compound which has a thiazole or oxazole structure. Patent reference 19: 2-permutation thiazole derivative is indicated by the international disclosure/[00th] No. 45635 pamphlet. However, neither disclosure of the compound which the compound of this official report has a carbamoyl group at the end of the substituent of the 2nd place of a thiazole ring, and has the structure like this invention compound, nor the publication of the purport which suggests it is found. Moreover, the compound of this official report is useful as an antimicrobial agent and a painkiller, and the publication which suggests it is not found as well as the disclosure about the usefulness as a PTP1B inhibitor, either.

[0014] Patent reference 20: The 2-ANIRINO-4-phenyl thiazole derivative is indicated by the ** table No. 504039 [2000 to] official report. However, neither disclosure of the compound which the compound of this official report has a phenyl group for the ANIRINO radical permuted by the 2nd place of a thiazole ring by the hydroxyl group or the carboxyl group in the 4th place, has a substituent in the 2nd place of this phenyl group of the 4th place, and has the structure like this invention compound, nor the publication of the purport which suggests it is found. Moreover, the compound of this official report is useful as a CRF (corticotropin releasing factor) antagonist, and the publication which suggests it is not found as well as the disclosure about the usefulness as a PTP1B inhibitor, either.

[0015] Patent reference 21: In JP,4-154773,A, it is a general formula [0016].

[Formula 2]

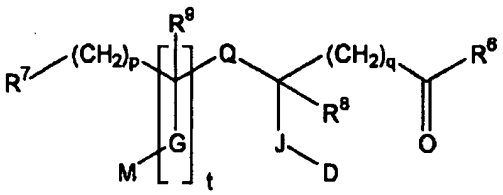


[0017] the inside of [type, and R1 and R2 are the same -- or -- differing -- a hydrogen atom and a halogen atom -- A low-grade alkyl group, a phenyl group, a permutation phenyl group, a pyridyl radical, or a permutation pyridyl radical R3 is a hydroxyl group, a lower alkoxy group, or -N (R5) (R6) (among a formula). R5 and R6 are the same -- or -- differing -- a hydrogen atom or a low-grade alkyl group -- being shown -- the thiazole derivative shown in the radical shown by] R4 indicates a hydrogen atom or a low-grade alkyl group, and X indicates the amino group, an amide group, a carbonyl group, an alkylene group, an oxygen atom, or a sulfur atom to be is indicated. However, there is no disclosure of the compound which has the structure like this invention compound in this official report, and the publication of the purport which suggests it is not found, either. Moreover, the compound of this official report is useful as an anti-inflammatory agent, and the publication which suggests it is not found as well as the disclosure about the usefulness as a PTP1B inhibitor, either.

[0018] Patent reference 22: 4-phenyl thiazole derivative is indicated by the international disclosure/ [94th] No. 08982 pamphlet. However, neither disclosure of the compound which the compound of this official report has a phenyl group in the 4th place of a thiazole ring, has substituents, such as a halogen, in the 2nd place of this phenyl group of the 4th place, and has the structure like this invention compound, nor the publication of the purport which suggests it is found. Moreover, the compound of this official report is useful as a pest control agent, and the publication which suggests it is not found as well as the disclosure about the usefulness as a PTP1B inhibitor, either.

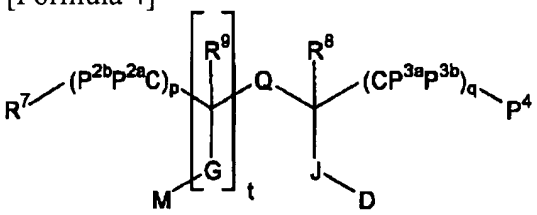
[0019] Patent reference 23: In an international disclosure/[02nd] No. 39997 pamphlet, it is a general formula [0020].

[Formula 3]



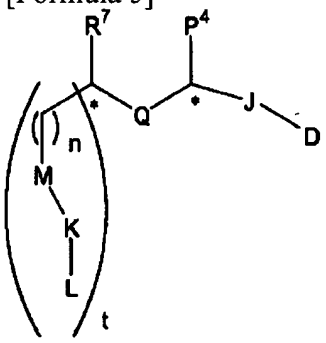
[0021] As for R6, R7 among [type a hydroxyl group or a protection nature prodrug part A hydrogen atom, A carboxy group, an arylamino carbonyl group, an aroyl radical, an aryl group, An alkylamino carbonyl group, an aminocarbonyl radical, an alkenyl amino carboxy group, A hydroxyl group, an alkoxy group, the ether, a thiol, an amino-group content heterocycle radical, or a protection nature prodrug part R8 the hydrogen atom or alkyl group which may combine with D and may form a ring In R9, Q a low-grade alkyl group or a hydrogen atom Association, an oxygen atom, a sulfur atom, CR3OH, CR3SH, CR3NR3aR3b, NR3, n (CR3R3a), O(CR3R3b) n or (CR3R3a) nO(CR3bR3c) n (among a formula) n shows the integer of 0 or 1 thru/or 3. Independently R3, R3a, R3b, and R3c, respectively A hydrogen atom, The straight chain which may be permuted, annular, or the C1-6 alkyl group of a branched chain, A C2-6 alkenyl radical, an acyl group, an arylated alkyl radical, an aryloxy carbonyl group, an arylamino carbonyl group, an arylated alkyl sulfonyl group, or an aryl group -- being shown -- In M, J a support part for a connection part association, an alkylene group, an alkenylene group, or alkynylene group [G] The hydrogen atom, alkoxy group which D may combine with G, M, or Q, and may form a ring, t is a general formula [0022] to] and the list p indicates the integer of 0 or 1 thru/or 5, and q indicates the integer of 0 or 1 thru/or 3 to be for 0 or 1 about an amine, an alkyl group, an alkenyl radical, an alkynyl group, an aryl group, or a hetero aryl group.

[Formula 4]



[0023] The inside of [type, the prodrug part which P4 cuts [a carboxy group and], COOP4', (CH2) 1-4SP4' or C(O) NP4 -- 'P4" -- R7 -- a hydrogen atom -- A carboxy group, the low-grade alkyl ester which may be permuted, low-grade alkenyl ester, The ester, the arylamino carbonyl group which the 2nd amine permuted by low-grade alkyl added, An aroyl radical, an aryl group, an alkylamino carbonyl group, an aminocarbonyl radical, COOR7', CONR7'R7", a hydroxyl group, the ether, a thiol, The amino group, 1 (CH2)-4SR7', and a heterocycle radical or the prodrug part which can be cut P4' and P4 -- ", R7', and R7" -- respectively -- independently -- a hydrogen atom -- C1-6 alkyl group, a C2-6 alkenyl radical, C2-6 alkynyl group, or the aryl group that may be permuted In R8, R9 covalent bond with a hydrogen atom, an alkyl group, or D a low-grade alkyl group or a hydrogen atom Q Association, an oxygen atom, a sulfur atom, CR3OH, CR3SH, CR3NR3aR3b, NR3, n (CR3R3a), O(CR3R3b) n, or (CR3R3a) nO (CR3bR3c) n (among a formula) n shows the integer of 0 or 1 thru/or 3. Independently R3, R3a, R3b, and R3c, respectively A hydrogen atom, The straight chain or branched chain alkenyl radical of the straight chain of C 1-6 which may be permuted or a branched chain alkyl group, and C 2-6, An aryloxy carbonyl group, an arylamino carbonyl group, an arylated alkyl sulfonyl group, the ring of C 3-8 which may be permuted with the arylated alkyl radical, the acyl group which may be permuted, the aryl group, or a maximum of 4 hetero atom -- being shown -- Independently P2a, P2b, P3a, and P3b, respectively A hydrogen atom or the straight chain which may be permuted, In G, for a branched chain or annular C1-5 alkyl group, M a connection part a support part J shows association, an alkylene group, an alkenylene group, or alkynylene group. Whether D shows a hydrogen atom, an alkyl group, an alkenyl radical, an alkynyl group, or an aryl group Or G, It may combine with M or Q and a ring may be formed. In t, p 0 or 1 the integer of 0 or 1 thru/or 5 The compound in which q is shown by] which shows the integer of 0

or 1 thru/or 3 is indicated. As an example of the support part in each general formula, -NR'R", -CONR'R", - S (O) 2 NR'R ", -S(O)0-2R', -NR'R", - O(CR'R")0-2CF3, -COR', -CO2R', or -OR' (among a formula) Independently R' and R", respectively A hydrogen atom, C1-6 alkyl group, a C2-6 alkenyl radical, C2-6 alkynyl group or the aryl group which may be permuted -- being shown -- covalent bond and C1-6 alkyl group are indicated for the thiazole radical and oxazole radical which have the aryl group or hetero aryl group permuted as substituents as an example of a connection part, respectively.
[0024] Furthermore, a general formula [0025]
[Formula 5]



[0026] the inside of [type, and M -- a ring radical, a heterocycle radical, or CONR'R" (the inside of a formula, and R' --) Independently R", respectively A hydrogen atom, C1-6 alkyl group, a C2-6 alkenyl radical, C2-6 alkynyl group or the aryl group which may be permuted -- being shown -- Q Association, an oxygen atom, a sulfur atom, CR3OH, CR3SH, CR3NR3aR3b, NR3, n (CR3R3a), O(CR3R3b) n, or (CR3R3a) nO(CR3bR3c) n (among a formula) n shows the integer of 0 or 1 thru/or 3. Independently R3, R3a, R3b, and R3c, respectively A hydrogen atom, The branched chain which may be permuted, annular, or the C1-6 alkyl group of a straight chain, A C2-6 alkenyl radical, an acyl group, an arylated alkyl radical, an aryloxy carbonyl group, an arylamino carbonyl group, an arylated alkyl sulfonyl group, or an aryl group -- being shown -- K is chosen independently -- secondary -- L is independently chosen in a connection [degree] part -- secondary -- a support [degree] part P4 A hydrogen atom, a carboxy group, 1(CH2)-4SP4', the prodrug part that can be cut, R7 COOP4' or CONP4'P4" A hydrogen atom, a carboxy group, an aroyl radical, an aryl group, COOR7', and C(O) NR7 -- 'R7" -- A hydroxyl group, the ether, a thiol, 1(CH2)-4SR7', and a heterocycle radical or the prodrug part which can be cut P4' and P4 -- ", R7', and R7" -- respectively -- independently -- a hydrogen atom -- C1-6 alkyl group, a C2-6 alkenyl radical, C2-6 alkynyl group, or the aryl group that may be permuted In n, D the integer of 0 or 1 thru/or 4 A hydrogen atom, an alkyl group, an alkoxy group, An alkenyl radical, an amine, a hydroxyl group, an alkynyl group, an aryl group, or a hetero aryl group the compound shown by] which shows 0 or 1 indicates t -- having -- **** -- secondary -- a connection [degree] part -- covalent bond -- secondary -- it is indicated in the support [degree] part that the aryl group which may be permuted is included, respectively.
[0027] However, there is no disclosure of the compound which has the structure like this invention compound in this official report, and the publication of the purport which suggests it is not found, either. Moreover, the compound of this official report is useful as angiotensin-converting-enzyme (ACE) -2 modifier, and the publication which suggests it is not found as well as the disclosure about the usefulness as a PTP1B inhibitor, either.
[0028]
[Patent reference 1] International disclosure/[00th] No. 17211 pamphlet [the patent reference 2] Patent Publication Heisei No. 508919 [11 to] official report [the patent reference 3] U.S. Pat. No. 5,770,620 description [the patent reference 4] International disclosure/[98th] No. 27092 pamphlet [the patent reference 5] U.S. Pat. No. 6,080,772 description [the patent reference 6] International disclosure/[99th] No. 58522 pamphlet [the patent reference 7] International disclosure/[99th] No. 58511 pamphlet [the patent reference 8] International disclosure/[99th] No. 58521 pamphlet [the patent reference 9] U.S.

Pat. No. 6,110,962 description [the patent reference 10] International disclosure/[99th] No. 58518 pamphlet [the patent reference 11] International disclosure/[99th] No. 61419 pamphlet [the patent reference 12] International disclosure/[99th] No. 58520 pamphlet [the patent reference 13] International disclosure/[99th] No. 61435 pamphlet [the patent reference 14] U.S. Pat. No. 6,103,708 description [the patent reference 15] U.S. Pat. No. 6,110,963 description [the patent reference 16] U.S. Pat. No. 6,001,867 description [the patent reference 17] U.S. Pat. No. 6,057,316 description [the patent reference 18] U.S. Pat. No. 6,063,815 description [the patent reference 19] International patent/[00th] No. 45635 pamphlet [the patent reference 20] ** table No. 504039 [2000 to] official report [the patent reference 21] JP,4-154773,A [the patent reference 22] International disclosure/[94th] No. 08982 pamphlet [the patent reference 23] International disclosure/[02nd] No. 39997 pamphlet [nonpatent literature 1] J. Biol.Chem., 1995, the 270th volume, p.7724-7730 [nonpatent literature 2] J. Biochem. (Tokyo), 1998, the 123rd volume, p.813-820 [nonpatent literature 3] Science, 1999, the 283rd volume, p.1544-1548 [0029]

[Problem(s) to be Solved by the Invention] The object of this invention is having the outstanding PTP1B inhibitory action and offering a compound useful as a remedy of diseases, such as diabetic medicine, a hyperlipidemia remedy or obesity, and a neurodegenerative disease. Moreover, the object of this invention is offering a PTP1B inhibitor, diabetic medicine, and a hyperlipidemia remedy.

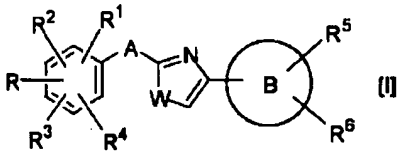
[0030]

[Means for Solving the Problem] In order to attain the above-mentioned object, as a result of repeating research wholeheartedly, this invention persons have the PTP1B inhibitory action excellent in the azole compound shown by the following general formula [I], and came to complete a header and this invention for it being useful as a PTP1B inhibitor, diabetic medicine, and a hyperlipidemia remedy. This invention relates to the compound shown in following [1] thru/or [54], and its remedy application.

[0031] [1] General formula [I]

[0032]

[Formula 6]



(I)

[0033] W shows a sulfur atom or an oxygen atom among [type, and;R is (1)-COOR7 (among a formula). R7 is (2)-X1-A1-COOR7 (among a formula) which shows a hydrogen atom or a low-grade alkyl group. X1 is -O-, -N(R15)-, or -S(O) p. - (R15 shows a hydrogen atom or a low-grade alkyl group among a formula) (3) tetrazolyl groups are shown. p -- 0, 1, or 2 -- being shown -- or it is shown, A1 shows a low-grade alkylene group and R7 shows a hydrogen atom or a low-grade alkyl group, R1, R2, R3, and R4 Independently, respectively (1) hydrogen atom, (2) halogen atom, (3) hydroxyl groups, (4) The low-grade cycloalkyl alkyloxy radical which may be permuted, the aralkyloxy radical by which (5) permutations may be carried out, (6) A cyano group, (7) nitro groups, (8) low-grade alkyl group, (9) low-grade halo alkyl group, (10) A lower alkoxy group or (11) low-grade haloalkoxy radical is shown, and;A is -(CH2) m-X. - (among a formula) X is -N(R8)-, -C(R9) (R10)-, -CO-, or -CO-N (R8). - (among a formula) R8 shows a hydrogen atom, -SO two R16 (R16 shows a low-grade alkyl group or an aryl group), or a low-grade alkyl group. The low-grade alkyl group concerned is a lower alkoxy group, an aryloxy group, and -N (R11) (R12) (R11 and R12). It becomes together with the nitrogen atom which shows a hydrogen atom or a low-grade alkyl group, or they combine independently, respectively. 5 which may contain at least one hetero atom chosen from the group which furthermore consists of a nitrogen atom, an oxygen atom, and a sulfur atom - 7 member heterocycle may be formed. You may permute by the substituent chosen from the group which consists of a carboxy group, a low-grade cycloalkyl radical, and an aryl group that may be permuted. R9 and R10 Independently, it may become together with the carbon atom which shows a hydrogen atom or a low-grade alkyl group, or they

combine, and low-grade cycloalkane may be formed, respectively. It is shown. or 5 which may contain at least one hetero atom chosen from the group which becomes together with the carbon atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle -- you may form -- m -- the integer of 0 or 1 thru/or 3 -- being shown -- the radical expressed -- being shown --;B -- an aryl group or an aromatic series heterocycle radical -- being shown --;R5 -- (1) hydrogen atom -- (2) A halogen atom, (3) low-grade alkyl group, (4) lower alkoxy groups, (5) A cyano group, (6) nitro groups, (7) low-grade halo alkyl group, or (8)-S(O) r-R17 (R17 shows a low-grade alkyl group or an aryl group) r -- 0, 1, or 2 -- being shown -- being shown --;R6 -(Y) s1-(A2) s-Z (s1 and s among a formula) 0 or 1 is shown independently, respectively. Y -O-, -S(O) t-, - N(R13)-, -N(R14)-CO-, -N(R14)-SO2-, - SO2-N(R14)-, -C(R18) (R19)-, or -CO - (among a formula) t -- 0, 1, or 2 -- being shown -- R13 -- (1) hydrogen atom and (2) low-grade alkyl group (the low-grade alkyl group concerned -- (a) low-grade cycloalkyl radical --) (b) You may permute by the substituent chosen from the group which consists of the aryl group which may be permuted, a heterocycle radical by which (c) permutation may be carried out, and a (d) hydroxyl group. (3) A low-grade alkenyl radical, (4) low-grade alkyl sulfonyl group, or (5) low-grade alkyl carbonyl group (the low-grade alkyl carbonyl group concerned may be permuted by the hydroxyl group or the lower alkoxy group) is shown. R14 shows a hydrogen atom or a low-grade alkyl group. R18 and R19 Independently, it may become together with the carbon atom which shows a hydrogen atom or a low-grade alkyl group, or they combine, and low-grade cycloalkane may be formed, respectively. It is shown. or 5 which may contain at least one hetero atom chosen from the group which becomes together with the carbon atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle -- you may form -- A2 shows the low-grade alkylene group which may be permuted by the low-grade cycloalkyl radical. Z (1) low-grade cycloalkyl radical (the low-grade cycloalkyl radical concerned may be permuted by the phenyl group which may be permuted), (2) -- an aryl group (the heterocycle radical which may be permuted by the substituent chosen from the group which the aryl group concerned becomes from (a) low-grade alkyl group and a low-grade alkyl carbonyl group --) (b) The low-grade cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and a low-grade alkyl group, (c) A carboxy group, (d) halogen atom, the (e) alkyl group, (f) low-grade halo alkyl group, (g) A low-grade alkylamino radical, (h) JI (low-grade alkyl) amino group, (i) You may permute by the substituent chosen from the group which consists of a low-grade alkylthio group and a (j) lower alkoxy group. (3) -- the aromatic series heterocycle radical which may be permuted, (4) indanyl radical, or (5) piperazinyl radical (the piperazinyl radical concerned -- the (a) phenyl group --) (b) Phenyl low-grade alkyl group, (c) -- it permutes by the substituent chosen from the group which consists of the benzoyl and (d) phenyl low-grade alkoxy carbonyl group which may be permuted by the halogen atom -- having -- **** -- the azole compound shown by] which shows the radical expressed, or its prodrug -- Or the salt which can be permitted on those remedies.

[0034] [2] In a general formula [I], W shows a sulfur atom or an oxygen atom, and;R is (1)-COOR7 (among a formula). R7 is (2)-X1-A1-COOR7 (among a formula) which shows a hydrogen atom or C1-4 alkyl group. X1 is -O-, -N(R15)-, or -S(O) p. - (R15 shows a hydrogen atom or C1-4 alkyl group among a formula) (3) tetrazolyl groups are shown. p -- 0, 1, or 2 -- being shown -- independently R1, R2, R3, and R4, respectively, or it is shown, A1 shows C1-4 alkylene group and R7 shows a hydrogen atom or C1-4 alkyl group (1) A hydrogen atom, (2) halogen atom, (3) hydroxyl groups, the C3-7 cycloalkyl C1-4 alkyloxy radical by which (4) permutations may be carried out, (5) The aralkyloxy radical which may be permuted, (6) cyano groups, (7) nitro groups, (8) C1-4 alkyl group, a (9) C1-4 halo alkyl group, (10) C1-4 alkoxy group, or a (11) C1-4 haloalkoxy radical is shown, and;A is -(CH2) m-X. - (among a formula) X is -N(R8)-, -C(R9) (R10)-, -CO-, or -CO-N (R8). - (among a formula) R8 shows a hydrogen atom, -SO two R16 (R16 shows C1-6 alkyl group or an aryl group), or C1-6 alkyl group. The C1-6 alkyl group concerned is C1-4 alkoxy group, an aryloxy group, and -N (R11) (R12) (R11 and R12). Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or 5 which may contain at least one hetero atom chosen from the group which becomes together with the nitrogen atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member

heterocycle may be formed. You may permute by the substituent chosen from the group which consists of a carboxy group, a C3-7 cycloalkyl radical, and an aryl group that may be permuted. R9 and R10 Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or it may become together with the carbon atom which they combine, and three to C7 cycloalkane may be formed. It is shown. or 5 which may contain at least one hetero atom chosen from the group which becomes together with the carbon atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle -- you may form -- m -- the integer of 0 or 1 thru/or 3 -- being shown -- the radical expressed -- being shown --;B -- an aryl group or an aromatic series heterocycle radical -- being shown --;R5 -- (1) hydrogen atom -- (2) A halogen atom, (3) C1-4 alkyl group, (4) C1-4 alkoxy group, (5) A cyano group, (6) nitro groups, a (7) C1-4 halo alkyl group, or (8)-S (O) r-R17 (R17 shows C1-6 alkyl group or an aryl group) r -- 0, 1, or 2 -- being shown -- being shown --;R6 -(Y) s1-(A2) s-Z (s1 and s among a formula) 0 or 1 is shown independently, respectively. Y -O-, -S (O) t-, - N(R13)-, -N(R14)-CO-, -N(R14)-SO2-, - SO2-N(R14)-, -C(R18) (R19)-, or -CO - (among a formula) t -- 0, 1, or 2 -- being shown -- R13 -- (1) hydrogen atom and (2) C1-4 alkyl group (the C1-4 alkyl group concerned -- a (a) C3-7 cycloalkyl radical --) (b) You may permute by the substituent chosen from the group which consists of the aryl group which may be permuted, a heterocycle radical by which (c) permutation may be carried out, and a (d) hydroxyl group. (3) A C2-4 alkenyl radical, a (4) C1-4 alkyl sulfonyl group, or a (5) C1-4 alkyl carbonyl group (the C1-4 alkyl carbonyl group concerned may be permuted by the hydroxyl group or the C1-4 alkoxy group) is shown. R14 shows a hydrogen atom or C1-4 alkyl group. R18 and R19 Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or it may become together with the carbon atom which they combine, and three to C7 cycloalkane may be formed. It is shown. or 5 which may contain at least one hetero atom chosen from the group which becomes together with the carbon atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle -- you may form -- A2 shows the C1-4 alkylene group which may be permuted by the C3-7 cycloalkyl radical. Z A (1) C3-7 cycloalkyl radical (the C3-7 cycloalkyl radical concerned may be permuted by the phenyl group which may be permuted by the halogen atom), (2) -- an aryl group (the heterocycle radical which may be permuted by the substituent chosen from the group which the aryl group concerned becomes from (a) C1-4 alkyl group and a C1-4 alkyl carbonyl group --) (b) The C3-7 cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (c) A carboxy group, (d) halogen atom, (e) C1-8 alkyl group, (f) A C1-4 halo alkyl group, a (g) C1-4 alkylamino radical, (h) You may permute by the substituent chosen from the group which consists of the JI (one to C4 alkyl) amino group, (i) C1-4 alkylthio group, and (j) C1-4 alkoxy group. (3) -- an aromatic series heterocycle radical (the heterocycle radical by which the aromatic series heterocycle radical concerned may be permuted by (a) C1-4 alkyl group --) (b) The aryl group which may be permuted by C1-6 alkyl group, (c) halogen atom, or the C1-4 halo alkyl group, (d) A halogen atom, a (e) C1-4 halo alkyl group, the (f) carboxy group, (g) You may permute by the substituent chosen from the group which consists of a C3-7 cycloalkyl radical and (h) C1-4 alkoxy group. (4) -- an indanyl radical or (5) piperazinyl radical (the piperazinyl radical concerned -- the (a) phenyl group --) (b) Phenyl C1-4 alkyl group, (c) -- it permutes by the substituent chosen from the group which consists of the benzoyl and the (d) phenyl C1-4 alkoxy carbonyl group which may be permuted by the halogen atom -- having -- **** -- the azole compound given in [1] in which the radical expressed is shown, or its prodrug -- Or the salt which can be permitted on those remedies.

[0035] [3] W is a sulfur atom or an oxygen atom, and R is (1)-COOR7 (among a formula). R7 is (2)-X1-A1-COOR7 (among a formula) which shows a hydrogen atom. (3) tetrazolyl groups are shown. Or X1 shows -O-, A1 shows C1-4 alkylene group and R7 shows a hydrogen atom, R1, R2, R3, and R4 Independently, respectively (1) hydrogen atom, (2) halogen atom, (3) hydroxyl groups, (4) The aralkyloxy radical by which the C3-7 cycloalkyl C1-4 alkyloxy radical which may be permuted, or (5) permutations may be carried out is shown, and;A is -(CH2) m-X. - (among a formula) X is -N(R8)-, -C (R9) (R10)-, or -CO. - (among a formula) R8 shows a hydrogen atom or C1-6 alkyl group, and the C1-6 alkyl group concerned is C1-4 alkoxy group, an aryloxy group, and -N (R11) (R12) (R11 and R12).

Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or 5 which may contain at least one hetero atom chosen from the group which becomes together with the nitrogen atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle may be formed. You may permute by the substituent chosen from the group which consists of a carboxy group, a C3-7 cycloalkyl radical, and an aryl group that may be permuted. R9 and R10 Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or it may become together with the carbon atom which they combine, and three to C7 cycloalkane may be formed. It is shown. or 5 which may contain at least one hetero atom chosen from the group which becomes together with the carbon atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle -- you may form -- m -- the integer of 0 or 1 thru/or 3 -- being shown -- the radical expressed -- being shown --;B -- an aryl group or an aromatic series heterocycle radical -- being shown --;R5 -- (1) hydrogen atom -- (2) A halogen atom, (3) C1-4 alkyl group, or (4) C1-4 alkoxy group is shown, and;R6 are -(Y) s1-(A2) s-Z (s1 and s among a formula). 0 or 1 is shown independently, respectively. Y -O-, -S(O) t-, - N(R13)-, -N(R14)-CO-, or -N (R14)-SO2 - (among a formula) t -- 0, 1, or 2 -- being shown -- R13 -- (1) hydrogen atom and (2) C1-4 alkyl group (the C1-4 alkyl group concerned -- a (a) C3-7 cycloalkyl radical --) (b) You may permute by the substituent chosen from the group which consists of the aryl group which may be permuted, a heterocycle radical by which (c) permutation may be carried out, and a (d) hydroxyl group. (3) A C2-4 alkenyl radical, a (4) C1-4 alkyl sulfonyl group, or a (5) C1-4 alkyl carbonyl group (the C1-4 alkyl carbonyl group concerned may be permuted by the hydroxyl group or the C1-4 alkoxy group) is shown. It is shown and A2 shows the C1-4 alkylene group which may be permuted by the C3-7 cycloalkyl radical. R14 -- a hydrogen atom or C1-4 alkyl group -- being shown -- Z A (1) C3-7 cycloalkyl radical (the C3-7 cycloalkyl radical concerned may be permuted by the phenyl group), (2) -- an aryl group (the heterocycle radical by which the aryl group concerned may be permuted by (a) C1-4 alkyl group or the C1-4 alkyl carbonyl group --) (b) The C3-7 cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (c) A carboxy group, (d) halogen atom, (e) C1-8 alkyl group, (f) A C1-4 halo alkyl group, a (g) C1-4 alkylamino radical, and (h) JI (one to C4 alkyl) amino group, (i) Even if it permutes by the substituent chosen from the group which consists of C1-4 alkylthio group and (j) C1-4 alkoxy group, it is good (3) aromatic-series heterocycle radical (the aromatic series heterocycle radical concerned). (a) You may permute by the substituent chosen from the group which consists of a phenyl group which may be permuted by the heterocycle radical, (b) C1-4 alkyl group and (c) halogen atom, or the C1-4 halo alkyl group. (4) -- an indanyl radical or (5) piperazinyl radical (the piperazinyl radical concerned -- the (a) phenyl group --) (b) -- it permutes by the substituent chosen from the group which consists of phenyl C1-4 alkyl group and a (c) phenyl C1-4 alkoxy carbonyl group -- you may have -- the salt which can be permitted on the azole compound given in [2] in which the radical expressed is shown, its prodrug, or those remedies.

[0036] [4] The azole compound given [given W is a sulfur atom] in [3] given m is 0 or 1, its prodrug, or the salt which can be permitted on those remedies.

[5] A is -(CH2) m-X. - (the inside of a formula and X are -N(R8)- (among a formula)) R8 shows a hydrogen atom or C1-6 alkyl group, and the C1-6 alkyl group concerned is C1-4 alkoxy group, an aryloxy group, and -N (R11) (R12) (R11 and R12). Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or 5 which may contain at least one hetero atom chosen from the group which becomes together with the nitrogen atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle may be formed. It is shown. it permutes by the substituent chosen from the group which consists of a carboxy group, a C3-7 cycloalkyl radical, and an aryl group that may be permuted -- having -- **** -- m -- 0 or 1 -- being shown -- the salt which can be permitted on the azole compound given in [4] in which the radical expressed is shown, its prodrug, or those remedies.

[0037] [6] The azole compound given in [5] given R is -X1-A1-COOR7 (the inside of a formula and each notation are as given in [3]), its prodrug, or the salt which can be permitted on those remedies.

[7] The azole compound given in [5] given R is -COOR7 (R7 shows a hydrogen atom among a formula), its prodrug, or the salt which can be permitted on those remedies.
[8] The azole compound given in [7] R1, R2, R3, and R4 given are hydrogen atoms, its prodrug, or the salt which can be permitted on those remedies.
[9] The azole compound given in [8] given B is a phenyl group, a thiazolyl radical, a pyridyl radical, a benzothiazolyl radical, a benzoimidazolyl radical, or a benzoxazolyl radical, its prodrug, or the salt which can be permitted on those remedies.
[10] The azole compound given in [9] given B is a phenyl group, its prodrug, or the salt which can be permitted on those remedies.
[11] The azole compound given in [10] R5 given is a hydrogen atom, its prodrug, or the salt which can be permitted on those remedies.
[0038] In R6 Z [12] A (1) C3-7 cycloalkyl radical (the C3-7 cycloalkyl radical concerned may be permuted by the phenyl group), (2) -- an aryl group (the heterocycle radical by which the aryl group concerned may be permuted by (a) C1-4 alkyl group or the C1-4 alkyl carbonyl group --) (b) The C3-7 cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (c) A carboxy group, (d) halogen atom, (e) C1-8 alkyl group, (f) A C1-4 halo alkyl group, a (g) C1-4 alkylamino radical, (h) Or you may permute by the substituent chosen from the group which consists of the JI (one to C4 alkyl) amino group, (i) C1-4 alkylthio group, and (j) C1-4 alkoxy group, it is (3) aromatic-series heterocycle radical (the aromatic series heterocycle radical concerned). (a) -- it permutes by the substituent chosen from the group which consists of a phenyl group which may be permuted by the heterocycle radical, (b) C1-4 alkyl group and (c) halogen atom, or the C1-4 halo alkyl group -- having -- **** -- the shown azole compound given in [11], or its prodrug -- Or the salt which can be permitted on those remedies.
[0039] [13] The heterocycle radical by which Z may be permuted by (a) C1-4 alkyl group or the C1-4 alkyl carbonyl group, (b) The C3-7 cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (c) A carboxy group, (d) halogen atom, (e) C1-8 alkyl group, (f) A C1-4 halo alkyl group, a (g) C1-4 alkylamino radical, (h) The azole compound or its prodrug given in [12] which shows the aryl group which may be permuted by the substituent chosen from the group which consists of the JI (one to C4 alkyl) amino group, (i) C1-4 alkylthio group, and (j) C1-4 alkoxy group, Or the salt which can be permitted on those remedies.
[0040] [14] The cyclohexyl radical or cyclopentylic group which may be permuted by the substituent chosen from the group which Z becomes from the (a) hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (b) -- the heterocycle radical (the heterocycle radical concerned -- a piperidinyl radical --) which may be permuted by C1-4 alkyl group or the C1-4 alkyl carbonyl group A mol HORINIRU radical, a piperazinyl radical, a tetrahydropyranyl group, The azole compound given in [13] which is the phenyl group permuted by the substituent chosen from the group which consists of (c) C1-8 alkyl group and it is chosen from the group which consists of a pyrrolidinyl radical and a pyrrolyl radical, its prodrug, or the salt which can be permitted on those remedies.
[15] The azole compound given in [14] in which the phenyl group permuted by the cyclohexyl radical which may be permuted by the substituent chosen from the group which Z becomes from a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group is shown, its prodrug, or the salt which can be permitted on those remedies.
[0041] [16] Set to R6 and Y is -O-, -N(R13)-, or -N(R14)-CO. - (among a formula) R13 shows a hydrogen atom, C1-4 alkyl group, or a C2-4 alkenyl radical. The C1-4 alkyl group concerned A C3-7 cycloalkyl radical, the aryl group which may be permuted, You may permute by the substituent chosen from the group which consists of the heterocycle radical and hydroxyl group which may be permuted. R14 -- a hydrogen atom or C1-4 alkyl group -- being shown -- the salt which is shown and can be permitted on an azole compound [13] whose s1 is 1, or given in [14], its prodrug, or those remedies.
[17] The salt which can be permitted in R6 on the azole compound given in [16] A2 given is a methylene group, its prodrug, or those remedies.

[18] An azole compound given in either [1] thru/or [17], its prodrug or the salt that can be permitted on those remedies, and the remedy constituent containing the support which can be permitted on a remedy.
[19] The remedy constituent for protein thyrosin phosphatase 1B inhibition which contains the azole compound of a publication, its prodrug or the salt that can be permitted on those remedies, and the support which can be permitted on a remedy in either [1] thru/or [17].
[20] The remedy constituent for a diabetes-mellitus therapy which contains the azole compound of a publication, its prodrug or the salt that can be permitted on those remedies, and the support which can be permitted on a remedy in either [1] thru/or [17].
[0042] [21] The remedy constituent for a hyperlipidemia therapy which contains the azole compound of a publication, its prodrug or the salt that can be permitted on those remedies, and the support which can be permitted on a remedy in either [1] thru/or [17].
[22] A remedy constituent given [for concomitant use with other hyperlipidemia remedies] in [18].
[23] The remedy constituent given in [22] given hyperlipidemia remedies are the drugs of a SUTACHIN system.
[24] The remedy constituent given in [23] chosen from the group which the drugs of a SUTACHIN system become from lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, and auction bus TACHIN.
[25] A remedy constituent given [for concomitant use with other diabetic medicine] in [18].
[0043] [26] A remedy constituent given [for concomitant use with the diabetic medicine chosen from the group which consists of the insulin secretagogue, sulfonyl urea medicine, sulfonamide medicine, BIGUANAIDO medicine, alpha GURUKO cytase inhibitor, insulin preparation, and insulin resistance improvement medicine] in [25].
[27] The remedy constituent given in [26] chosen from the group which diabetic medicine becomes from nateglinide, glimepiride, glibenclamide, gliclazide, acetohexamide, tolbutamide, glyclopyramide, tolazamide, glybuzole, metformin hydrochloride, buformin hydrochloride, voglibose, acarbose, an insulin, and pioglitazone hydrochloride.
[28] A remedy constituent given [for concomitant use with other hyperlipidemia remedies] in [20].
[29] The remedy constituent given in [28] given hyperlipidemia remedies are the drugs of a SUTACHIN system.
[30] The remedy constituent given in [29] chosen from the group which the drugs of a SUTACHIN system become from lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, and auction bus TACHIN.
[0044] [31] A remedy constituent given [for concomitant use with other diabetic medicine] in [20].
[32] A remedy constituent given [for concomitant use with the diabetic medicine chosen from the group which consists of the insulin secretagogue, sulfonyl urea medicine, sulfonamide medicine, BIGUANAIDO medicine, alpha GURUKO cytase inhibitor, insulin preparation, and insulin resistance improvement medicine] in [31].
[33] The remedy constituent given in [32] chosen from the group which diabetic medicine becomes from nateglinide, glimepiride, glibenclamide, gliclazide, acetohexamide, tolbutamide, glyclopyramide, tolazamide, glybuzole, metformin hydrochloride, buformin hydrochloride, voglibose, acarbose, an insulin, and pioglitazone hydrochloride.
[34] A remedy constituent given [for concomitant use with other hyperlipidemia remedies] in [21].
[35] The remedy constituent given in [34] given hyperlipidemia remedies are the drugs of a SUTACHIN system.
[0045] [36] The remedy constituent given in [35] chosen from the group which the drugs of a SUTACHIN system become from lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, and auction bus TACHIN.
[37] A remedy constituent given [for concomitant use with other diabetic medicine] in [21].
[38] A remedy constituent given [for concomitant use with the diabetic medicine chosen from the group which consists of the insulin secretagogue, sulfonyl urea medicine, sulfonamide medicine, BIGUANAIDO medicine, alpha GURUKO cytase inhibitor, insulin preparation, and insulin resistance

improvement medicine] in [37].
[39] The remedy constituent given in [38] chosen from the group which diabetic medicine becomes from nateglinide, glimepiride, glibenclamide, gliclazide, acetohexamide, tolbutamide, glyclopyramide, tolazamide, glybuzole, metformin hydrochloride, buformin hydrochloride, voglibose, acarbose, an insulin, and pioglitazone hydrochloride.
[40] The inhibition approach of protein thyrosin phosphatase 1B which includes medicating mammalian with the azole compound of a publication, its prodrug, or the salt that can be permitted on those remedies in either [1] of an effective dose thru/or [17].
[0046] [41] The diabetic therapy approach which includes medicating mammalian with the azole compound of a publication, its prodrug, or the salt that can be permitted on those remedies in either [1] of an effective dose thru/or [17].
[42] The therapy approach of hyperlipidemia which includes medicating mammalian with the azole compound of a publication, its prodrug, or the salt that can be permitted on those remedies in either [1] of an effective dose thru/or [17].
[43] The activity of the salt which can be permitted on the azole compound of a publication, its prodrug, or those remedies in either [1] for manufacturing a protein thyrosin phosphatase 1B inhibitor thru/or [17].
[44] The activity of the salt which can be permitted on the azole compound of a publication, its prodrug, or those remedies in either [1] for manufacturing diabetic medicine thru/or [17].
[45] The activity of the salt which can be permitted on the azole compound of a publication, its prodrug, or those remedies in either [1] for manufacturing hyperlipidemia **** thru/or [17].
[0047] [46] The commercial package containing the written object about the remedy constituent concerned which indicated that a remedy constituent and the remedy constituent concerned given in [18] should have been used or used for the inhibition application of protein thyrosin phosphatase 1B.
[47] The commercial package containing the written object about the remedy constituent concerned which indicated that a remedy constituent and the remedy constituent concerned given in [18] should have been used or used for a diabetic therapy application.
[48] The commercial package containing the written object about the remedy constituent concerned which indicated that a remedy constituent and the remedy constituent concerned given in [18] should have been used or used for the therapy application of hyperlipidemia.
[49] The therapy approach of hyperlipidemia which includes medicating mammalian with the azole compound of a publication, its prodrug, or the salt that can be permitted on those remedies, and medicating the mammalian concerned with other hyperlipidemia remedies of an effective dose in either [1] of an effective dose thru/or [17].
[50] The therapy approach given in [49] that hyperlipidemia remedies are the drugs of a SUTACHIN system.
[0048] [51] The therapy approach given in [50] chosen from the group which the drugs of a SUTACHIN system become from lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, and auction bus TACHIN.
[52] The diabetic therapy approach which includes medicating mammalian with the azole compound of a publication, its prodrug, or the salt that can be permitted on those remedies, and medicating the mammalian concerned with other diabetic medicine of an effective dose in either [1] of an effective dose thru/or [17].
[53] The therapy approach given in [52] chosen from the group which diabetic medicine becomes from the insulin secretagogue, sulfonyl urea medicine, sulfonamide medicine, BIGUANAIDO medicine, alpha GURUKO cytase inhibitor, insulin preparation, and insulin resistance improvement medicine.
[54] The therapy approach given in [53] chosen from the group which diabetic medicine becomes from nateglinide, glimepiride, glibenclamide, gliclazide, acetohexamide, tolbutamide, glyclopyramide, tolazamide, glybuzole, metformin hydrochloride, buformin hydrochloride, voglibose, acarbose, an insulin, and pioglitazone hydrochloride.
[0049]

[Embodiment of the Invention] The definition like each substituent used in this description and each part is as follows. In this description, "C 1-6" shows that carbon numbers are 1 thru/or six pieces. A "halogen atom" is a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom, and is a fluorine atom or a chlorine atom preferably.
[0050] A "low-grade alkyl group" expresses a carbon number 1 thru/or the straight chain of 6, or a branched chain alkyl group, and a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical, an isopentyl radical, a neopentyl radical, a tert-pentyl radical, 1-ethyl propyl group, a hexyl group, etc. are specifically mentioned. They are a carbon number 1 thru/or the straight chain of 4, or a branched chain alkyl group preferably. Preferably, in R1, R2, R3, R4, R5, R7, R9, R10, R11, R12, R13, R14, R15, R18, and R19, it is C1-4 alkyl group, and is C1-6 alkyl group in R8, R16, and R17.
[0051] A "low-grade halo alkyl group" expresses the halo alkyl group by which the carbon number 1 thru/or the straight chain of 6, or the branched chain alkyl group was permuted by the "halogen atom" of the above-mentioned definition, and fluoro methyl group, difluoromethyl group, trifluoromethyl radical, bromomethyl radical, chloro methyl group, 1, 2-dichloro methyl group, 2, and 2-dichloro methyl group, 2 and 2, 2-trifluoro ethyl group, etc. are specifically mentioned. It is a carbon number 1 thru/or the straight chain of 4, or a branched chain halo alkyl group preferably, and is a trifluoromethyl radical especially preferably. Preferably, in R1, R2, R3, R4, and R5, it is a C1-4 halo alkyl group.
[0052] A "low-grade alkylene group" expresses a carbon number 1 thru/or the straight chain of 6, or a branched chain alkylene group, and a methylene group, ethylene, a trimethylene radical, a propylene radical, a tetramethylen radical, a pentamethylene radical, a hexamethylene radical, etc. are mentioned. It is a carbon number 1 thru/or the straight chain of 4, or a branched chain alkylene group preferably, and is a methylene group especially preferably. Preferably, in A1 and A2, it is C1-4 alkylene group.
[0053] A "lower alkoxy group" expresses a carbon number 1 thru/or the straight chain of 6, or a branched chain alkoxy group, and a methoxy group, an ethoxy radical, a propoxy group, an isopropoxy group, a butoxy radical, an iso butoxy radical, a tert-butoxy radical, a pentyloxy radical, a hexyloxy radical, etc. are specifically mentioned. They are a carbon number 1 thru/or the straight chain of 4, or a branched chain alkoxy group preferably. Preferably, in R1, R2, R3, R4, and R5, it is C1-4 alkoxy group.

[0054] As for a "low-grade haloalkoxy radical", a carbon number 1 thru/or the straight chain of 6, or a branched chain alkoxy group expresses the haloalkoxy radical permuted by the "halogen atom" of the above-mentioned definition, and fluoro methyloxy radical, difluoro methyloxy radical, trifluoro methyloxy radical, bromomethyl oxy-radical, chloro methyloxy radical, 1, 2-dichloro methyloxy radical, 2, and 2-dichloro methyloxy radical, 2 and 2, 2-trifluoro ethyloxy radical, etc. are specifically mentioned. It is a carbon number 1 thru/or the straight chain of 4, or a branched chain haloalkoxy radical preferably, and is a trifluoro methyloxy radical especially preferably. Preferably, in R1, R2, R3, and R4, it is a C1-4 haloalkoxy radical.
[0055] An "aryl group" expresses a carbon number 6 thru/or the aromatic hydrocarbon radical of 14, and a phenyl group, a naphthyl group, biphenylyl radicals (for example, 2-biphenylyl radical, 3-biphenylyl radical, 4-biphenylyl radical, etc.), an anthryl radical, etc. are specifically mentioned. It is a phenyl group and a biphenylyl radical preferably, and is a phenyl group more preferably. Preferably, in R16, R17, B, and Z, it is C6-14 aryl group.
[0056] An "aryloxy group" is an aryloxy group which has the "aryl group" of said definition as an "aryl part", and a phenoxy group, a naphthyloxy radical, a biphenylyl oxy-radical (for example, 2-biphenylyl oxy-radical, 3-biphenylyl oxy-radical, 4-biphenylyl oxy-radical), an anthryl oxy-radical, etc. are specifically mentioned. It is a phenoxy group and a biphenylyl oxy-radical preferably, and is a phenoxy group more preferably.
[0057] An "aralkyloxy radical" is an aralkyloxy radical which has the "aryl group" of said definition as an "aryl part", and has a carbon number 1 thru/or the straight chain of 4, or a branched chain alkyl group as an "alkyl part", and a benzyloxy radical, a phenethyloxy radical, 3-phenyl propyloxy radical, etc. are specifically mentioned. It is a benzyloxy radical preferably. Preferably, in R1, R2, R3, and R4, it is a

C6-14 aryl C1-4 alkyloxy radical.
[0058] "Low-grade cycloalkyl radicals" is a carbon number 3 thru/or a cycloalkyl radical of 7, and is specifically a cyclo propyl group, cyclo butyl, a cyclopentylic group, a cyclohexyl radical, and a cycloheptyl radical. It is a carbon number 5 thru/or the cycloalkyl radical of 7 preferably, and is a cyclohexyl radical especially preferably. Preferably, in Z, it is a C3-7 cycloalkyl radical.
[0059] With a "low-grade cycloalkyl alkyloxy radical" It has the "low-grade cycloalkyl radical" of said definition as a "cycloalkyl part." It is the cycloalkyl alkyloxy radical which has the "low-grade alkyl group" of said definition as an "alkyl part". Specifically A cyclopropyl methyl oxy-radical, a cyclo butyl methyloxy radical, a cyclopentyl methyloxy radical, A cyclohexyl methyloxy radical, a cycloheptyl methyloxy radical, 2-cyclo propylethyl oxy-radical, 2-cyclo butyl ethyloxy radical, 2-cyclopentyl ethyloxy radical, 2-cyclohexyl ethyloxy radical, a 2-cycloheptyl ethyloxy radical, 3-cyclohexyl propyloxy, 4-cyclohexyl butyloxy radical, etc. are mentioned. Preferably, it is a C3-7 cycloalkyl C1-4 alkyloxy radical, and it is more desirable, is a C5-7 cycloalkyl C1-4 alkyloxy radical, and is a cyclohexyl C1-4 alkyloxy radical especially preferably. Preferably, in R1, R2, R3, and R4, it is a C5-7 cycloalkyl C1-4 alkyloxy radical.
[0060] A "low-grade alkenyl radical" expresses a carbon number 2 thru/or the straight chain of 6, or a branched chain alkenyl radical, and a vinyl group, 1-propenyl radical, an allyl group, a 1-methyl-2-propenyl radical, 1-butenyl group, 2-butenyl group, 3-butenyl group, 1-pentenyl radical, 2-pentenyl radical, a 1-hexenyl radical, a 2-hexenyl radical, etc. are specifically mentioned. They are a carbon number 2 thru/or the straight chain of 4, or a branched chain alkenyl radical preferably. Preferably, in R13, it is a C2-4 alkenyl radical.
[0061] A "low-grade alkyl sulfonyl group" is an alkyl sulfonyl group which has the "low-grade alkyl group" of said definition as an "alkyl part", and a methyl sulfonyl group, an ethyl sulfonyl group, a propyl sulfonyl group, an isopropyl sulfonyl group, a butyl sulfonyl group, an isobutyl sulfonyl group, a sec-butyl sulfonyl group, a tert-butyl sulfonyl group, a pentyl sulfonyl group, an isopentyl sulfonyl group, a tert-pentyl sulfonyl group, a hexyl sulfonyl group, etc. are specifically mentioned. It is a C1-4 alkyl sulfonyl group preferably. Preferably, in R13, it is a C1-4 alkyl sulfonyl group.
[0062] A "low-grade alkyl carbonyl group" is an alkyl carbonyl group which has the "low-grade alkyl group" of said definition as an "alkyl part", and an acetyl group, a propionyl radical, a butyryl radical, an isobutyl radical, a valeryl radical, an iso valeryl radical, a pivaloyl radical, a PENTA noil radical, a hexa noil radical, etc. are specifically mentioned. It is the C1-4 alkyl carbonyl group whose "alkyl part" is the straight chain or branched chain alkyl group of 1 thru/or 4 preferably. Preferably, in R13, it is a C1-4 alkyl carbonyl group.
[0063].R is the radical shown by -COOR7 or -X1-A1-COOR7, and when R7 is a hydrogen atom, this carboxy group may form the salt. As a salt, alkali-metal salts (for example, potassium salt, sodium salt, etc.), alkaline-earth-metal salts (for example, a calcium salt, magnesium salt, etc.), etc. are mentioned. It is an alkali-metal salt preferably.
[0064] As for the tetrazolyl group in R, the tetrazole ring may form the alkali-metal salt. Potassium salt, sodium salt, etc. are mentioned as this alkali-metal salt.
[0065] The "low-grade cycloalkanes" which R9 and R10 may become together with the carbon atom which they combine, and they may form is a carbon number 3 thru/or the cycloalkane of 7, and is specifically a cyclopropane, a cyclobutane, a cyclopentane, a cyclohexane, and cycloheptane. It is a carbon number 5 thru/or the cycloalkane of 7 preferably, and they are a cyclopentane or a cyclohexane especially preferably.
[0066] "Further R9 and R10 may become together with the carbon atom which they combine, and they may form. A nitrogen atom, With 5 which may contain at least one hetero atom chosen from the group which consists of an oxygen atom and a sulfur atom - 7 member heterocycle" Preferably, it is "5 - 7 member heterocycle of the saturation which may contain 1-3 hetero atoms chosen from the group which consists of a nitrogen atom, an oxygen atom, and a sulfur atom further", tetrahydropyran, Jiang, etc. are specifically mentioned, and it is tetrahydropyran especially preferably.
[0067] The "aromatic series heterocycle radical" in B, "Contain 1-3 hetero atoms chosen from the group

which consists of a nitrogen atom, an oxygen atom, and a sulfur atom. 5 - 14 member aromatic series heterocycle radical of a monocycle or the condensed ring" is expressed. Specifically A furil radical, a thienyl group, a pyrrolyl radical, an oxazolyl radical, an iso oxazolyl radical, A thiazolyl radical, an iso thiazolyl radical, an imidazolyl radical, a pyrazolyl radical, A pyridyl radical, a pilus DAJINIRU radical, a pyrimidinyl group, a pyrazinyl radical, an indolyl radical, An iso indolyl radical, a benzofuranyl radical, a benzothienyl group, a benzoimidazolyl radical, A benzothiazolyl radical, a benzoxazolyl radical, an in DORIJINIRU radical, a quinolyl radical, an iso quinolyl radical, a chinae-cortex ZORINIRU radical, a SHINNORINIRU radical, a kino KISARINIRU radical, a phthalazinyl radical, an acridinyl radical, a FENAJINIRU radical, a naphthyridinyl group, etc. are mentioned. Contain 1-3 hetero atoms preferably chosen from the group which consists of "nitrogen atom, an oxygen atom, and a sulfur atom. It is 5 - 10 member aromatic series heterocycle radical of a monocycle or the condensed ring". A furil radical, A thienyl group, a pyrrolyl radical, an oxazolyl radical, an iso oxazolyl radical, a thiazolyl radical, An iso thiazolyl radical, an imidazolyl radical, a pyrazolyl radical, a pyridyl radical, a pilus DAJINIRU radical, A pyrimidinyl group, a pyrazinyl radical, an indolyl radical, an iso indolyl radical, a benzofuranyl radical, a benzothienyl group, a benzoimidazolyl radical, a benzothiazolyl radical, a benzoxazolyl radical, etc. are mentioned. They are a thiazolyl radical, a pyridyl radical, a benzothiazolyl radical, a benzoimidazolyl radical, and a benzoxazolyl radical especially preferably.

[0068] The "low-grade cycloalkyl alkyloxy radical" in R1, R2, R3, and R4 may be permuted by 1-3 substituents chosen from degrees. As this substituent, a halogen atom, C1-4 alkyl group, a C1-4 halo alkyl group, C1-4 alkoxy group, a carboxy group, a hydroxyl group, a cyano group, a nitro group, the amino group, an alkoxy carbonyl group (the carbon numbers of an alkoxy part are 1 thru/or 4), etc. are mentioned. In R1, R2, R3, and R4, 2-cyclohexyl ethyloxy radical is mentioned as desirable "low-grade cycloalkyl alkyloxy radical which may be permuted."

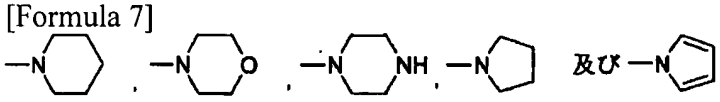
[0069] The "aralkyloxy radical" in R1, R2, R3, and R4 may be permuted by 1-3 substituents chosen from degrees. As this substituent, a halogen atom, C1-4 alkyl group, a C1-4 halo alkyl group, C1-4 alkoxy group, a carboxy group, a hydroxyl group, a cyano group, a nitro group, the amino group, an alkoxy carbonyl (carbon numbers of alkoxy part are 1 thru/or 4) radical, etc. are mentioned. A desirable substituent is a carboxy group. In R1, R2, R3, and R4, a benzyloxy radical, a carboxy benzyloxy radical, etc. are mentioned as desirable "aralkyloxy radical which may be permuted."

[0070] The "low-grade alkyl group" in R8 is a lower alkoxy group, an aryloxy group, and -N (R11) (R12) (R11 and R12). It becomes together with the nitrogen atom which shows a hydrogen atom or a low-grade alkyl group, or they combine independently, respectively. 5 which may contain at least one hetero atom chosen from the group which furthermore consists of a nitrogen atom, an oxygen atom, and a sulfur atom - 7 member heterocycle may be formed. You may permute by the substituent chosen from the group which consists of a carboxy group, a low-grade cycloalkyl radical, and an aryl group that may be permuted.

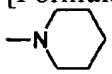
[0071] "The aryl group which may be permuted" which is a substituent on the "low-grade alkyl group" in R8 may be permuted by 1-3 substituents chosen from degrees. As this substituent, a halogen atom, C1-4 alkyl group, a C1-4 halo alkyl group, C1-4 alkoxy group, a carboxy group, a hydroxyl group, a cyano group, a nitro group, the amino group, an alkoxy carbonyl group (the carbon numbers of an alkoxy part are 1 thru/or 4), etc. are mentioned. Desirable substituents are a halogen atom and a C1-4 halo alkyl group.

[0072] R11 and R12 may become together with the nitrogen atom which they combine, and may form. With "5 which may contain at least one hetero atom chosen from the group which consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle" Preferably, it is "the saturation or the partial saturation 5 - 7 member heterocycle" which may contain 1-3 hetero atoms chosen from the group which consists of a nitrogen atom, an oxygen atom, and a sulfur atom further, and, specifically, is [0073].

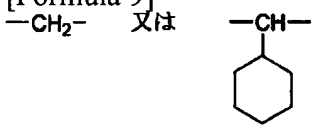
[Formula 7]

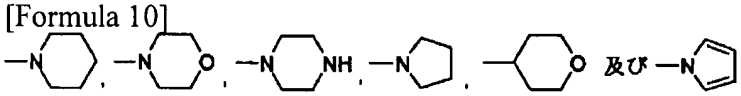


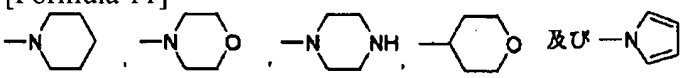
[0074] since -- the heterocycle chosen from the becoming group -- it is -- especially -- desirable --
[0075]
[Formula 8]



[0076] It comes out.
[0077] The "low-grade alkyl group" in R13 may be permuted by the substituent chosen from the group which consists of a C3-7 cycloalkyl radical, the aryl group which may be permuted, a heterocycle radical which may be permuted, and a hydroxyl group.
[0078] "The aryl group which may be permuted" which is a substituent on the "low-grade alkyl group" in R13 may be permuted by 1-3 substituents chosen from degrees. As this substituent, a halogen atom, C1-4 alkyl group, a C1-4 halo alkyl group, C1-4 alkoxy group, a carboxy group, a hydroxyl group, a cyano group, a nitro group, the amino group, an alkoxy carbonyl group (the carbon numbers of an alkoxy part are 1 thru/or 4), etc. are mentioned. A desirable substituent is a halogen atom or a C1-4 halo alkyl group.
[0079] "The heterocycle radical which may be permuted" which is a substituent on the "low-grade alkyl group" in R13 It is "5 - 7 member heterocycle radical of the saturation containing 1-3 hetero atoms chosen from the group which consists of a nitrogen atom, an oxygen atom, and a sulfur atom, or partial saturation" preferably. Specifically A furil radical, a thienyl group, a pyrrolyl radical, an oxazolyl radical, an iso oxazolyl radical, A thiazolyl radical, an iso thiazolyl radical, an imidazolyl radical, a pyrazolyl radical, A pyridyl radical, a pilus DAJINIRU radical, a pyrimidinyl group, a pyrazinyl radical, a tetrahydro furil radical, A tetrahydro thienyl group, a pyrrolidinyl radical, a PIRAZORIJINIRU radical, an imidazolidinyl radical, An oxazolidinyl radical, a thiazolysinyl radical, a tetrahydropyranyl group, the dioxa nil radical, a piperidinyl radical, a piperazinyl radical, a mol HORINIRU radical, etc. are mentioned, and it is a tetrahydropyranyl group preferably.
[0080] "The heterocycle radical which may be permuted" which is a substituent on the "low-grade alkyl group" in R13 may be permuted by 1-3 substituents chosen from degrees. As this substituent, a halogen atom, C1-4 alkyl group, a C1-4 halo alkyl group, C1-4 alkoxy group, a carboxy group, a hydroxyl group, a cyano group, a nitro group, the amino group, an alkoxy carbonyl group (the carbon numbers of an alkoxy part are 1 thru/or 4), etc. are mentioned.
[0081] The "low-grade alkyl carbonyl group" in R13 may be permuted by the hydroxyl group or the lower alkoxy group.
[0082] As a lower alkoxy group which is a substituent on the "low-grade alkyl carbonyl group" in R13, the "lower alkoxy group" of said definition is mentioned, and it is C1-4 alkoxy group preferably.
[0083] The "low-grade cycloalkanes" which R18 and R19 may become together with the carbon atom which they combine, and may form is a carbon number 3 thru/or the cycloalkane of 7, and is specifically a cyclopropane, a cyclobutane, a cyclopentane, a cyclohexane, and cycloheptane. It is a carbon number 5 thru/or the cycloalkane of 7 preferably, and they are a cyclopentane or a cyclohexane especially preferably.
[0084] "Further R18 and R19 may become together with the carbon atom which they combine, and may form. A nitrogen atom, With 5 which may contain at least one hetero atom chosen from the group which consists of an oxygen atom and a sulfur atom - 7 member heterocycle" Preferably, it is "5 - 7 member heterocycle of the saturation which may contain 1-3 hetero atoms chosen from the group which consists of a nitrogen atom, an oxygen atom, and a sulfur atom further", tetrahydropyran, Jiang, etc. are specifically mentioned, and it is tetrahydropyran especially preferably.
[0085] The low-grade alkylene group in A2 may be permuted by the low-grade cycloalkyl radical. As this low-grade cycloalkyl radical, a carbon number 3 thru/or the cycloalkyl radical of 7 are mentioned, and they are specifically a cyclo propyl group, cyclo butyl, a cyclopentylic group, a cyclohexyl radical, and a cycloheptyl radical. It is a carbon number 5 thru/or the cycloalkyl radical of 7 preferably, and is a

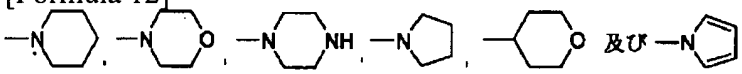
cyclohexyl radical especially preferably.
[0086] As "a low-grade alkylene group which may be permuted by the low-grade cycloalkyl radical" in A2, it is "the C1-4 alkylene group which may be permuted by the C3-7 cycloalkyl radical" preferably, and is [0087] more preferably.
[Formula 9]


[0088] It comes out.
[0089] The "low-grade cycloalkyl radical" in Z is a C3-7 cycloalkyl radical preferably, is a cyclopentylic group or a cyclohexyl radical more preferably, and is a cyclohexyl radical still more preferably.
[0090] The "low-grade cycloalkyl radical" in Z (a) halogen atom, (b) C1-6 alkyl group, (c) A C1-4 halo alkyl group, the (d) carboxy group, a (e) C3-7 cycloalkyl radical, (f) You may permute by the C1-4 alkoxy group, the heterocycle radical which may be permuted by (g) C1-4 alkyl group, or the (h) phenyl group, and the phenyl group concerned may be permuted by further 1 thru/or five halogen atoms (preferably 1 thru/or three pieces). The substituent of this "low-grade cycloalkyl radical" is a phenyl group which may be preferably permuted by 1 thru/or three halogen atoms, and is a phenyl group more preferably.
[0091] The "aryl groups" in Z is a phenyl group and a biphenylyl radical (for example, 2-biphenylyl radical, 3-biphenylyl radical, 4-biphenylyl radical) preferably, and is phenyl groups more preferably.
[0092] The "aryl group" in Z may be permuted by 1 thru/or five substituents (preferably 1 thru/or three pieces) chosen from degrees.
(a) The heterocycle radical which may be permuted by the substituent chosen from the group which consists of a low-grade alkyl group and a low-grade alkyl carbonyl group, (b) The low-grade cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and a low-grade alkyl group, (c) A carboxy group, (d) halogen atom, the (e) alkyl group, (f) low-grade halo alkyl group, (g) low-grade alkylamino radical, (h) JI (low-grade alkyl) amino group, (i) low-grade alkylthio group, and (j) lower alkoxy group.
[0093] The "heterocycle radical" in "the heterocycle radical which may be permuted by the substituent chosen from the group which consists of a low-grade alkyl group and a low-grade alkyl carbonyl group" It is "5 - 7 member heterocycle radical of the saturation containing 1-3 hetero atoms chosen from the group which consists of a nitrogen atom, an oxygen atom, and a sulfur atom, or partial saturation" preferably. Specifically A furil radical, a thienyl group, a pyrrolyl radical, an oxazolyl radical, an iso oxazolyl radical, A thiazolyl radical, an iso thiazolyl radical, an imidazolyl radical, a pyrazolyl radical, A pyridyl radical, a pilus DAJINIRU radical, a pyrimidinyl group, a pyrazinyl radical, a tetrahydro furil radical, A tetrahydro thienyl group, a pyrrolidinyl radical, a PIRAZORIJINIRU radical, an imidazolidinyl radical, an oxazolidinyl radical, a thiazolysinyl radical, a tetrahydropyranyl group, the dioxa nil radical, a piperidinyl radical, a piperazinyl radical, a mol HORINIRU radical, etc. are mentioned. A piperidinyl radical, a mol HORINIRU radical, a piperazinyl radical, a pyrrolidinyl radical, a pyrrolyl radical, and a tetrahydropyranyl group are mentioned preferably, and it is [0094] more preferably.
[Formula 10]


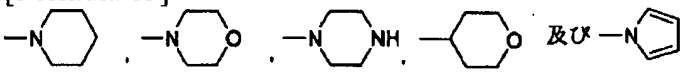
[0095] since -- the radical chosen from the becoming group -- it is -- especially -- desirable -- [0096]
[Formula 11]


[0097] since -- it is the radical chosen from the becoming group. As a substituent on the "heterocycle radical" concerned, they are C1-4 alkyl group or a C1-4 alkyl carbonyl group (the carbon numbers of an alkyl part are 1 thru/or 4) preferably.
[0098] The "low-grade cycloalkyl" in "the low-grade cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and a low-grade alkyl group" is a C3-7 cycloalkyl radical preferably, and is a cyclohexyl radical more preferably. The "low-grade cycloalkyl radical" concerned may be permuted by 1 thru/or five substituents (preferably 1 thru/or three pieces) chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and a low-grade alkyl group. As a substituent on the "low-grade cycloalkyl radical" concerned, they are a hydroxyl group, an oxo-radical, a halogen atom, or C1-4 alkyl group preferably.
[0099] As a "halogen atom" which is a substituent on the "aryl group" in Z, the "halogen atom" of the above-mentioned definition is mentioned, and they are a fluorine atom, a chlorine atom, or a bromine atom preferably.
[0100] The "alkyl group" which is a substituent on the "aryl group" in Z is a carbon number 1 thru/or the straight chain of 8, or a branched chain alkyl group, and, specifically, a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical, an isopentyl radical, a neopentyl radical, a tert-pentyl radical, 1-ethyl propyl group, a hexyl group, a heptyl radical, 1-propyl butyl, an octyl radical, etc. mentioned
[0101] As a "low-grade halo alkyl group" which is a substituent on the "aryl group" in Z, the "low-grade halo alkyl group" of the above-mentioned definition is mentioned, and it is a C1-4 halo alkyl group preferably.
[0102] The "low-grade alkylamino radical" which is a substituent on the "aryl group" in Z is an alkylamino radical which has the "low-grade alkyl group" of the above-mentioned definition as an "alkyl part", and, specifically, a methylamino radical, an ethylamino radical, a propylamino radical, an isopropylamino radical, a butylamino radical, the isobutyl amino group, a sec-butylamino radical, a tert-butylamino radical, a pentylamino radical, the isopentyl amino group, the neopentyl amino group, a tert-pentylamino radical a hexylamino radical, etc. be mentioned Preferably, it is a C1-4 alkylamino radical.
[0103] The "JI (low-grade alkyl) amino group" which is a substituent on the "aryl group" in Z It is the dialkylamino radical which has the "low-grade alkyl group" of the above-mentioned definition as an "alkyl part". Specifically A dimethylamino radical, a diethylamino radical, a dipropylamino radical, a diisopropylamino radical, A dibutylamino radical, the diisobutyl amino group, the JI (sec-butyl) amino group, The JI (tert-butyl) amino group, the dipentyl amino group, the diisopentyl amino group, The JI (tert-pentyl) amino group, the dihexyl amino group, an N-ethyl-N-methylamino radical, an N-methyl-N-propylamino radical, an N-ethyl-N-propylamino radical, etc. are mentioned. Preferably, it is a JI (one to C4 alkyl) amino group.
[0104] The "low-grade alkylthio group" which is a substituent on the "aryl group" in Z It is the alkylthio group which has the "low-grade alkyl group" of the above-mentioned definition as an "alkyl part". Specifically A methylthio radical, an ethyl thio radical, a propyl thio radical, an isopropyl thio radical, A butyl thio radical, an isobutyl thio radical, a sec-butyl thio radical, a tert-butyl thio radical, a pentyl thio radical, an isopentyl thio radical, a neopentyl thio radical, a tert-pentyl thio radical, a hexyl thio radical, etc. are mentioned. Preferably, it is C1-4 alkylthio group.
[0105] The "lower alkoxy group" which is a substituent on the "aryl group" in Z is a "lower alkoxy group" of the above-mentioned definition, and is C1-4 alkoxy group preferably.
[0106] The "aromatic series heterocycle radical" in Z preferably "Contain 1-3 hetero atoms chosen from the group which consists of a nitrogen atom, an oxygen atom, and a sulfur atom. It is 5 - 10 member aromatic series heterocycle radical of a monocycle or the condensed ring". A furil radical, A thienyl group, a pyrrolyl radical, an oxazolyl radical, an iso oxazolyl radical, a thiazolyl radical, An iso thiazolyl radical, an imidazolyl radical, a pyrazolyl radical, a pyridyl radical, a pilus DAJINIRU radical, A pyrimidinyl group, a pyrazinyl radical, an indolyl radical, an iso indolyl radical, a benzofuranyl radical, a benzothienyl group, a benzoimidazolyl radical, a benzothiazolyl radical, a benzoxazolyl radical, etc.

are mentioned. They are a thiazolyl radical or a pyridyl radical especially preferably.
[0107] The "aromatic series heterocycle radical" in Z may be permuted by 1 thru/or five substituents (preferably 1 thru/or three pieces) chosen from degrees.
(a) The aryl group which may be permuted by the heterocycle radical which may be permuted by C1-4 alkyl group, (b) C1-6 alkyl group, (c) halogen atom, or the C1-4 halo alkyl group, (d) halogen atom, a (e) C1-4 halo alkyl group, the (f) carboxy group, a (g) C3-7 cycloalkyl radical, and (h) C1-4 alkoxy group. As this substituent, it is the aryl group which may be permuted by (a) heterocycle radical, (b) C1-6 alkyl group, (c) halogen atom, or the C1-4 halo alkyl group preferably.
[0108] The "heterocycle radical" which is a substituent on the "aromatic series heterocycle radical" in Z It is "5 - 7 member heterocycle radical of the saturation containing 1-3 hetero atoms chosen from the group which consists of a nitrogen atom, an oxygen atom, and a sulfur atom, or partial saturation" preferably. Specifically A furil radical, a thienyl group, a pyrrolyl radical, an oxazolyl radical, an iso oxazolyl radical, A thiazolyl radical, an iso thiazolyl radical, an imidazolyl radical, a pyrazolyl radical, A pyridyl radical, a pilus DAJINIRU radical, a pyrimidinyl group, a pyrazinyl radical, a tetrahydro furil radical, A tetrahydro thienyl group, a pyrrolidinyl radical, a PIRAZORIJINIRU radical, an imidazolidinyl radical, an oxazolidinyl radical, a thiazolysinyl radical, a tetrahydropyranyl group, the dioxa nil radical, a piperidinyl radical, a piperazinyl radical, a mol HORINIRU radical, etc. are mentioned. A piperidinyl radical, a mol HORINIRU radical, a piperazinyl radical, a tetrahydropyranyl group, a pyrrolidinyl radical, and a pyrrolyl radical are mentioned preferably, and it is [0109] more preferably.
[Formula 12]



[0110] since -- the radical chosen from the becoming group -- it is -- especially -- desirable -- [0111]
[Formula 13]



[0112] It comes out.
[0113] "The aryl group which may be permuted by the halogen atom or the C1-4 halo alkyl group" which is a substituent on the "aromatic series heterocycle radical" in Z is "a phenyl group which may be permuted by the halogen atom or the C1-4 halo alkyl group" preferably.
[0114] The "piperazinyl radical" in Z may be permuted by 1 thru/or five substituents (preferably 1 thru/or three pieces) chosen from degrees.
(a) A phenyl group, (b) phenyl low-grade alkyl group, the benzoyl that may be permuted by (c) halogen atom, and (d) phenyl low-grade alkoxy carbonyl group.
[0115] The "phenyl low-grade alkyl group" which is a substituent on the "piperazinyl radical" in Z is a phenyl alkyl group which has the "low-grade alkyl group" of the above-mentioned definition as an "alkyl part", and, specifically, benzyl, a phenethyl radical, 1-phenylethyl radical, 3-phenylpropyl radical, etc. are mentioned. Preferably, it is phenyl C1-4 alkyl group.
[0116] "The benzoyl which may be permuted by the halogen atom" which is a substituent on the "piperazinyl radical" in Z is the benzoyl which may be preferably permuted by the "halogen atom" of 1 thru/or five above-mentioned definitions, and, specifically, chloro benzoyl, BUROMO benzoyl, etc. are mentioned.
[0117] The phenyl low-grade alkoxy carbonyl group which is a substituent on the "piperazinyl radical" in Z is a phenylalkoxy carbonyl group which has the "lower alkoxy group" of the above-mentioned definition as an "alkoxy part", and, specifically, a benzyloxycarbonyl radical etc. is mentioned. Preferably, it is a phenyl C1-4 alkoxy carbonyl group.
[0118] In a general formula [I], the desirable substituent is as follows. W is a sulfur atom preferably. R is -COOR7 (R7 shows a hydrogen atom among a formula) preferably. R1, R2, R3, and R4 are hydrogen

atoms preferably. A is -(CH2) m-X preferably. - (the inside of a formula and X are -N(R8)- (among a formula)) R8 shows a hydrogen atom or C1-6 alkyl group, and the C1-6 alkyl group concerned is C1-4 alkoxy group, an aryloxy group, and -N (R11) (R12) (R11 and R12). Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or 5 which may contain at least one hetero atom chosen from the group which becomes together with the nitrogen atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle may be formed. it permutes by the substituent chosen from the group which consists of a carboxy group, a C3-7 cycloalkyl radical, and an aryl group that may be permuted -- having -- **** -- being shown -- m -- the integer of 0 or 1 thru/or 3 -- being shown -- the radical expressed is shown. B is a phenyl group, a thiazolyl radical, a pyridyl radical, a benzothiazolyl radical, a benzoimidazolyl radical, or a benzoxazolyl radical preferably, and is a phenyl group more preferably. R5 is a hydrogen atom preferably.

[0119] Preferably Z A (1) C3-7 cycloalkyl radical (the C3-7 cycloalkyl radical concerned may be permuted by the phenyl group which may be permuted by the halogen atom), (2) -- an aryl group (the heterocycle radical by which the aryl group concerned may be permuted by (a) C1-4 alkyl group or the C1-4 alkyl carbonyl group --) (b) The C3-7 cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (c) A carboxy group, (d) halogen atom, (e) C1-8 alkyl group, (f) A C1-4 halo alkyl group, a (g) C1-4 alkylamino radical, (h) Or you may permute by the substituent chosen from the group which consists of the JI (one to C4 alkyl) amino group, (i) C1-4 alkylthio group, and (j) C1-4 alkoxy group, it is (3) aromatic-series heterocycle radical (the aromatic series heterocycle radical concerned). (a) -- it permutes by the substituent chosen from the group which consists of a phenyl group which may be permuted by the heterocycle radical, (b) C1-4 alkyl group and (c) halogen atom, or the C1-4 halo alkyl group -- having -- **** -- it is shown.

[0120] The heterocycle radical by which Z may be more preferably permuted by (a) C1-4 alkyl group or the C1-4 alkyl carbonyl group, (b) The C3-7 cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (c) A carboxy group, (d) halogen atom, (e) C1-8 alkyl group, (f) The aryl group which may be permuted by the substituent chosen from the group which consists of a C1-4 halo alkyl group, a (g) C1-4 alkylamino radical, a (h) JI (one to C4 alkyl) amino group, and (i) C1-4 alkylthio group is shown.

[0121] The cyclohexyl radical or cyclopentylic group which may be permuted by the substituent chosen from the group which Z becomes from the (a) hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group still more preferably, (b) -- the heterocycle radical (the heterocycle radical concerned -- a piperidinyl radical --) which may be permuted by C1-4 alkyl group or the C1-4 alkyl carbonyl group And it is chosen from the group which consists of a mol HORINIRU radical, a piperazinyl radical, a tetrahydropyranyl group, a pyrrolidinyl radical, and a pyrrolyl radical, the phenyl group permuted by the substituent chosen from the group which consists of (c) C1-8 alkyl group is shown.

[0122] Z shows the phenyl group permuted by the cyclohexyl radical which may be permuted by the substituent especially chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group preferably.

[0123] Setting to R6, Y is -O-, -N(R13)-, or -N(R14)-CO preferably. - (among a formula) R13 shows a hydrogen atom, C1-4 alkyl group, or a C2-4 alkenyl radical. the C1-4 alkyl group concerned is permuted by the substituent chosen from the group which consists of a C3-7 cycloalkyl radical, an aryl group which may be permuted, and a heterocycle radical which may be permuted -- having -- **** -- R14 -- a hydrogen atom or C1-4 alkyl group -- being shown -- it is shown and s1 shows 0 or 1. A2 is a methylene group preferably.

[0124] As long as "the salt which can be permitted on a remedy" forms the compound shown by the above-mentioned general formula [I], and a nonpoisonous salt, what kind of salt is sufficient as it. For example, inorganic-acid; or oxalic acid, such as a hydrochloric acid, a sulfuric acid, a phosphoric acid, and a hydrobromic acid, A malonic acid, a citric acid, a fumaric acid, a lactic acid, a malic acid, a

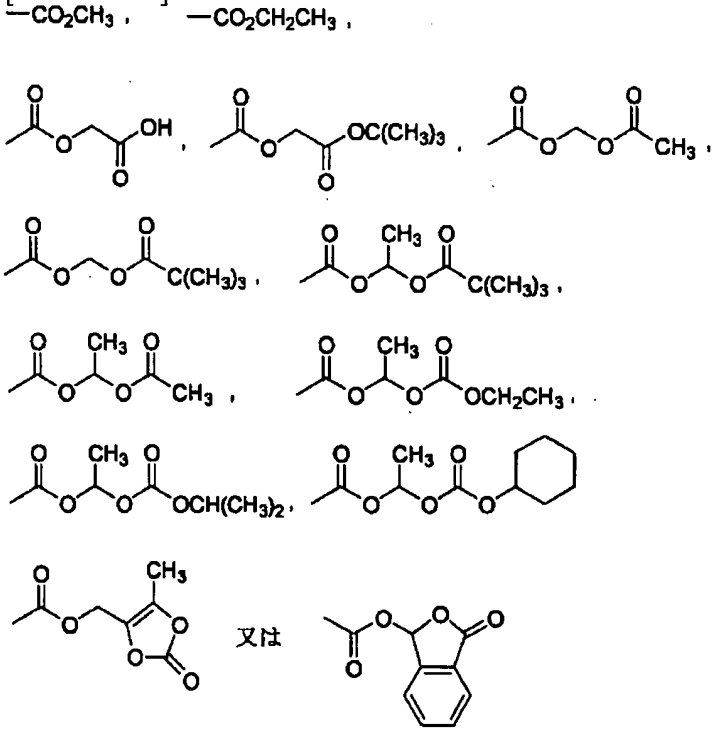
succinic acid, a tartaric acid, An acetic acid, trifluoroacetic acid, a gluconic acid, an ascorbic acid, methylsulfonic acid, Organic-acids [, such as a benzyl sulfonic acid,]; or a sodium hydroxide, a potassium hydroxide, Inorganic base; or monomethylamines, such as a calcium hydroxide, a magnesium hydroxide, and ammonium hydroxide, Diethylamine, triethylamine, triethanolamine, ethylenediamine, It can obtain by making it react with amino acid, such as organic base [, such as tris (hydroxymethyl) monomethylamine, guanidine, a choline, a cinchonine, and an N-methyl-D-glucamine,]; or a lysine, a histidine, an arginine, and an alanine. In addition, as for hydrated compound ****** of each compound, a hydrate and solvate are also included in this invention.

[0125] Moreover, various isomers exist in the compound shown by the above-mentioned general formula [I]. For example, when E bodies and Z body exist as a geometrical isomer and an asymmetric carbon atom exists, the enantiomer and diastereomer as a stereoisomer based on these exist. A tautomer may exist depending on the case. Therefore, these all isomers and those mixture are included by the range of this invention.

[0126] In addition, the prodrug and metabolite of the compound shown by the general formula [I] in this invention are also included. After having the radical which may be decomposed chemically [a "prodrug"] or in metabolic turnover and medicating a living body, it is the derivative of this invention compound in which it restores to the original compound and original drug effect is shown, and the complex and salt by covalent bond are included. For example, in a medicinal field, an ester derivative well-known as a prodrug can be used. The ester derivative in which the radical as which R is expressed in the following formulas is specifically shown is mentioned.

[0127]

[Formula 14]



[0128] The support permitted on well-known medicine manufacture usually in itself when using this invention compound as remedy pharmaceutical preparation, An excipient, a diluent, an extending agent, disintegrator, a stabilizer, a preservative, a buffer, an emulsifier, An aromatic, a coloring agent, a sweetening agent, a viscous agent, corrigent, a solubilizing agent, other additives, Specifically Alcohol, such as water, vegetable oil, ethanol, or benzyl alcohol, It mixes with carbohydrates, such as a polyethylene glycol, glycerol triacetate, gelatin, a lactose, and starch, magnesium stearate, talc, lanolin, vaseline, etc. A medicine can be prescribed for the patient by taking orally or parenteral systemic or

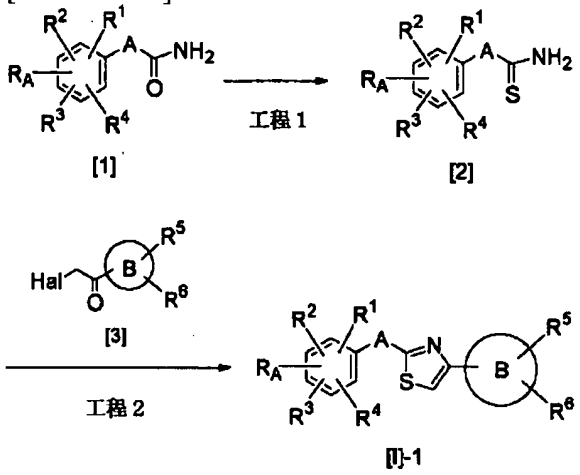
locally by making with a conventional method with gestalten, such as a tablet, a pill, powder, granulation, suppositories, injections, ophthalmic solutions, liquids and solutions, a capsule, the trochiscus, aerosols, elixirs, suspension, an emulsion, and syrups.
[0129] Although the dose of this invention compound changes with age, weight, a symptom, the disease that should be treated, medication methods, etc., it is the range of 50mg thru/or 800mg, and 1 time per one adult is usually medicated with 1 time per thru/or several times day.
[0130] The compound [I] of this invention Prevention or the remedy of a PTP1B inhibitor and diabetes mellitus, Prevention or the remedy of diabetic complications (myocardial infarction, cerebral infarction, etc. based on a retinopathy, a nephropathy, neuropathy, and arteriosclerosis), Mammalians (Homo sapiens, a mouse, a rat, a rabbit, a dog, a cat, a cow, Buta, ape, etc.) can be medicated as the prevention or the remedy of a disease with which prevention [of prevention or the remedy of hyperlipidemia obesity, a neurodegenerative disease, etc.] or remedy, and PTP1B intervenes.
[0131] The compound [I] of this invention is the object of prevention of diabetes mellitus or diabetic complications, or a therapy, and concomitant use administration can be carried out with other diabetic medicine at mammalian. The remedy of diabetic complications is also contained in "diabetic medicine" in this invention. Moreover, the compound [I] of this invention is the object of prevention of hyperlipidemia, or a therapy, and concomitant use administration can be carried out with other hyperlipidemia remedies at mammalian.
[0132] In concomitant use administration, the compound of this invention may be prescribed for the patient simultaneously with other diabetic medicine or other hyperlipidemia remedies (henceforth a concomitant use remedy), or may set and prescribe a time interval for the patient. In concomitant use administration, a medicine can be prescribed for the patient as the compound of this invention, and a remedy constituent containing a concomitant use remedy. Or the remedy constituent containing the compound of this invention and the remedy constituent containing a concomitant use remedy may be independently prescribed for the patient. Even if the route of administration of each remedy constituent is the same, they may differ.
[0133] the case of concomitant use administration -- the compound of this invention -- 1 time -- the dose of the range of 50mg thru/or 800mg -- it is -- 1 time per day -- or a medicine can be prescribed for the patient several times, or may be prescribed for the patient with a smaller dose. A concomitant use remedy can be prescribed for the patient with the usual dose in case they are used for prevention or the therapy of prevention or the therapy of diabetes mellitus or diabetic complications, or hyperlipidemia, or may be prescribed for the patient with a smaller dose.
[0134] As other diabetic medicine used for concomitant use administration, the insulin secretagogue, sulfonyl urea medicine, sulfonamide medicine, BIGUANAIDO medicine, alpha GURUKO cytase inhibitor, insulin preparation, insulin resistance improvement medicine, etc. are mentioned. For example, nateglinide, glimepiride, glibenclamide, gliclazide, acetohexamide, tolbutamide, glyclopyramide, tolazamide, glybuzole, metformin hydrochloride, buformin hydrochloride, voglibose, acarbose, an insulin, pioglitazone hydrochloride, etc. are used for concomitant use administration with this invention compound.
[0135] The drugs of a SUTACHIN system are mentioned as other hyperlipidemia remedies used for concomitant use administration. For example, lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, auction bus TACHIN, etc. are used for concomitant use administration with this invention compound.
[0136] Next, an example of the manufacture approach of the compound used in order to carry out this invention is explained. However, the manufacture approach of this invention compound is not limited to these. What is necessary is just to manufacture efficiently by the device of replacing the sequence of the each process and the process of introducing a protective group into a functional group if needed, and performing deprotection at an after process, even if unstated to this process. Moreover, what is necessary is just to perform processing after a reaction in each process by choosing suitably the approach used [preparative isolation / HPLC / isolation purification crystallization, recrystallization, a silica gel chromatography,] commonly, and combining that what is necessary is just to carry out by the approach

usually performed.

[0137] An one process process is an approach of manufacturing the compound [I] whose W is a sulfur atom.

Process 1 [0138]

[Formula 15]



[0139] (RA shows -COOR7' or -X1-A1-COOR7' (R7' shows a low-grade alkyl group) among a formula, Hal shows halogen atoms, such as a bromine atom and a chlorine atom, and each other notations are as said definition.)

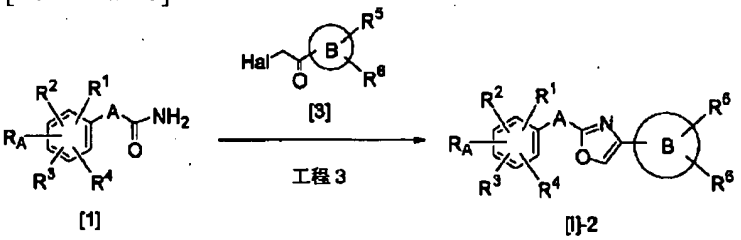
[0140] A compound [2] can be obtained by making process 1 compound [1] react with thiocarbonyl-ized agents, such as a Lawesson reagent and 5 sulfuration 2 Lynn, among a solvent. As a solvent, those mixed solvents, such as a tetrahydrofuran (THF), 1, 2-dimethoxyethane (DME), toluene, a xylene, chloroform, dichloromethane, and dioxane, are mentioned. 50 degrees C - 100 degrees C are suitable for reaction temperature.

[0141] [Compound I]-1 can be obtained by making process 2 compound [2] react with a compound [3] under existence of a base or nonexistence among a solvent and under heating. As a solvent, those mixed solvents, such as an acetonitrile, alcohols (a methanol, ethanol, isopropyl alcohol, etc.), THF and DME, and dioxane, are mentioned. A sodium hydrogencarbonate, a potassium hydrogencarbonate, etc. are mentioned as a base.

[0142] A two process process is an approach of manufacturing the compound [I] whose W is an oxygen atom.

Process 2 [0143]

[Formula 16]



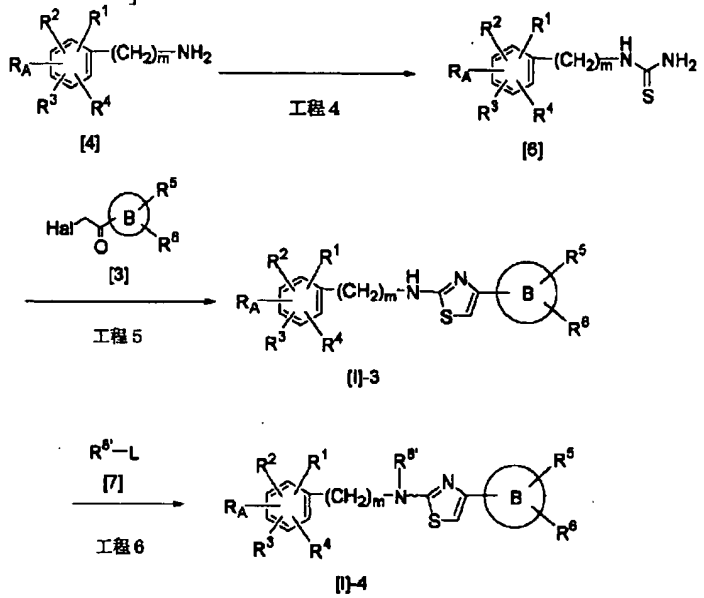
[0144] (Each notation is as said definition among a formula.)

[0145] [Compound I]-2 can be obtained by making process 3 compound [1] react with a compound [3] in a solvent and under heating. As a solvent, those mixed solvents, such as an acetonitrile, alcohols, xylenes (a methanol, ethanol, isopropyl alcohol, etc.), and toluene, are mentioned.

[0146] A three process process is an approach of manufacturing the compound [I] whose W is a sulfur atom and whose A is -(CH2) m-N(R8)-.

Process 3 [0147]

[Formula 17]



[0148] (R8' shows -SO two R16 or a low-grade alkyl group among a formula, and the low-grade alkyl group concerned may be permuted by the substituent chosen from the group which consists of a lower alkoxy group, an aryloxy group, -N (R11) (R12), a carboxy group, a low-grade cycloalkyl radical, and an aryl group that may be permuted.) L shows leaving groups, such as an iodine atom, a bromine atom, and a chlorine atom, and each other notations are as said definition.

[0149] Process 4 compound [4] can be made to be able to react with 1 and 1'-thio carbonyldiimidazole, thiophosgene, etc. under existence of a base or nonexistence among a solvent, and, subsequently a compound [6] can be obtained by making it react with ammonia. As a solvent, those mixed solvents, such as chloroform, dichloromethane, a dichloroethane, THF and DME, dioxane, and toluene, are mentioned. As a base, triethylamine, diisopropyl ethylamine, 1, a 8-diazabicyclo [5.4.0] undeca-7-en (DBU), sodium hydride, etc. are mentioned. -20 degrees C - 50 degrees C are suitable for reaction temperature.

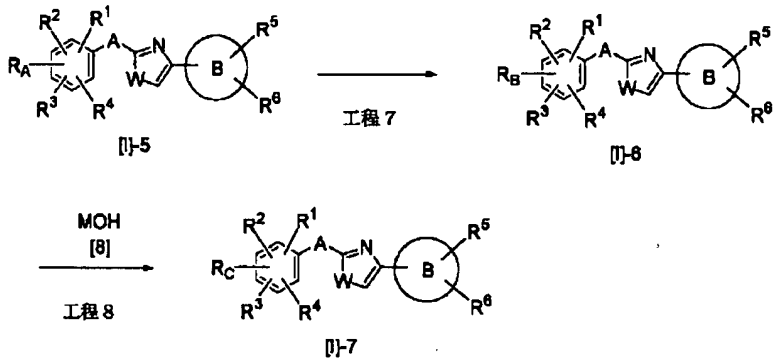
[0150] [Compound I]-3 can be obtained by making process 5 compound [6] react with a compound [3] under existence of a base or nonexistence among a solvent and under heating. As a solvent, those mixed solvents, such as an acetonitrile, alcohols (a methanol, ethanol, isopropyl alcohol, etc.), THF and DME, and dioxane, are mentioned. A sodium hydrogencarbonate, a potassium hydrogencarbonate, etc. are mentioned as a base.

[0151] Process 6 compound [I] [Compound I]-4 can be obtained by making -3 react with a compound [7] under existence of a base among a solvent. As a solvent, those mixed solvents, such as dimethylformamide, dimethylacetamide, THF and DME, dioxane, hexamethylphosphoramide (HMPA), and dimethyl sulfoxide (DMSO), are mentioned. As a base, sodium hydride, potassium carbonate, a sodium carbonate, etc. are mentioned. 0 degree C - 100 degrees C are suitable for reaction temperature.

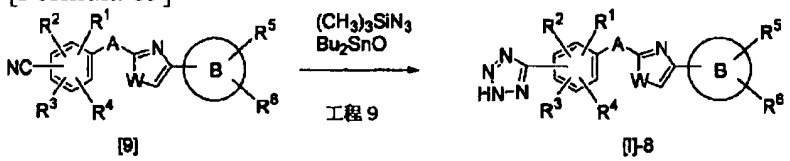
[0152] A four process process is an approach of manufacturing the compound [I] whose R7 is a hydrogen atom, or its salt, when R is -COOR7 or -X1-A1-COOR7.

Process 4 [0153]

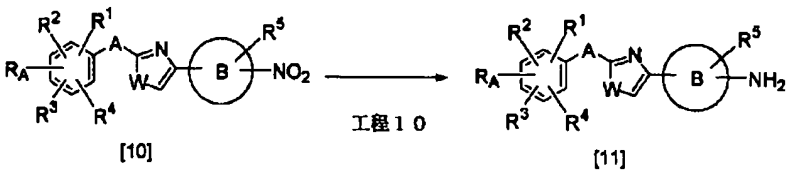
[Formula 18]

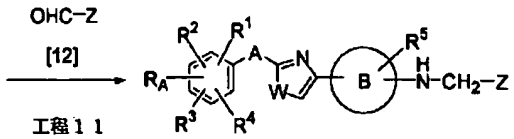


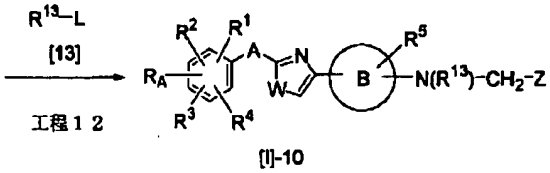
[0154] (RB shows -COOH or -X1-A1-COOH among a formula, RC shows -COOM or -X1-A1-COOM (M shows alkali metal), and each other notations are as said definition.)
[0155] Process 7 compound [I] [Compound I]-6 can be obtained by hydrolyzing -5. Hydrolysis can be performed according to a conventional method. For example, the approach of hydrolyzing under existence of an acid (Lewis acid being included) or a base is mentioned among a solvent. As a solvent, those mixed solvents, such as alcohols, tetrahydrofurans (a methanol, ethanol, isopropyl alcohol, etc.), dioxane, DME, N.N-dimethylformamide (DMF), DMSO, and water, are mentioned. As an acid, a hydrochloric acid, trifluoroacetic acid, a sulfuric acid, etc. are mentioned. As a base, an alkali-metal hydroxide, potassium carbonate (a sodium hydroxide, potassium hydroxide, etc.), a sodium carbonate, etc. are mentioned. Especially reaction temperature is not limited but can react under cooling thru/or heating.
[0156] Process 8 compound [I] [Compound I]-7 can be obtained by making -6 react with an alkali-metal hydroxide [8] according to a conventional method. Alkali-metal hydroxides are a sodium hydroxide, a potassium hydroxide, etc. This process can be performed in a solvent. As a solvent, those mixed solvents, such as alcohols, tetrahydrofurans (a methanol, ethanol, etc.), dioxane, and DME, are mentioned. Especially reaction temperature is not limited but can react under cooling thru/or heating.
[0157] A five process process is an approach of manufacturing the compound [I] whose R is a tetrazolyl group.
Process 5 [0158]
[Formula 19]



[0159] (Each notation is as said definition among a formula.)
[0160] [Compound I]-8 can be obtained by making the compound [9] manufactured by the process 9 aforementioned processes 1-3 and the same approach react with trimethylsilyl azide and dibutyl tin oxide among a solvent. As a solvent, those mixed solvents, such as toluene, a xylene, and benzene, are mentioned. 50 degrees C - 150 degrees C are suitable for reaction temperature.
[0161] A six process process is an approach of manufacturing the compound [I] whose R6 is -N(R13)-CH2-Z.
Process 6 [0162]
[Formula 20]



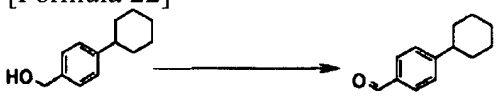




[0163] (Each notation is as said definition among a formula.)
[0164] A compound [11] can be obtained by returning process 10 compound [10]. Reduction can be performed according to a conventional method. For example, a compound [11] can be obtained by carrying out catalytic reduction of the compound [10] in a solvent and under catalyst existence and a hydrogen ambient atmosphere. As a solvent, alcohols, tetrahydrofurans (a methanol, ethanol, isopropyl alcohol, etc.), an acetic acid, etc. are mentioned. The palladium catalyst of palladium-carbon etc. is mentioned as a catalyst.
[0165] [Compound I]-9 can be obtained by making process 11 compound [11] react with a compound [12] under existence of a reducing agent. As a reducing agent, a thoria SETOKISHI sodium borohydride, hydrogenation cyano boron sodium (NaBH3CN), etc. are mentioned. 0 degree C - 40 degrees C are suitable for reaction temperature.
[0166] Process 12 compound [I] [Compound I]-10 can be obtained by making -9 react with a compound [13] under existence of a base among a solvent. This reaction can be performed by the same approach as the process 6 in a process 3.
[0167] In addition, the manufacture approach indicated on these descriptions is an example of the manufacture approach of this invention compound, and can be manufactured also about the compound except having explained above by combining a well-known conventional method in the field of synthetic organic chemistry.
[0168]
[Example] Next, this invention is not limited by these examples although the example of manufacture and an example explain concretely the compound shown by the general formula [I] concerning this invention, and its manufacture approach.
Example of manufacture 14-cyclohexyl benzaldehyde (1)4-cyclohexyl benzyl alcohol [0169]
[Formula 21]

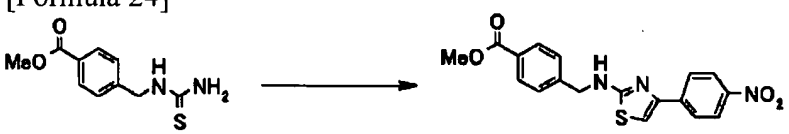
[0170] Under the nitrogen air current, after adding a tetrahydrofuran (1.2L, 15.0 v/w) to 4-cyclohexyl benzoic acid (80.0g, 0.382 mols), chloro carbonic acid isobutyl (52.0ml, 0.401 mols) was added. Under ice-cooling stirring, after adding triethylamine (56.0ml, 0.401 mols) to reaction mixture, it stirred by this ** for 30 minutes. Produced precipitate was carried out the ** exception. The above-mentioned filtrate was carefully added to the tetrahydrofuran (160ml, 2.0 v/w) suspension of the sodium borohydride (58.0g, 1.53 mols) prepared for another reactor under ice-cooling stirring under the nitrogen air current.

Distilled water (160ml, 2.0 v/w) was added under ice-cooling stirring 1.5 hours after room temperature stirring. 2N-hydrochloric acid (825ml, 4.3eq) was added after [of ice-cooling stirring] 20 minutes. Ethyl acetate (400ml) extracted after [of room temperature stirring] 30 minutes, and the organic layer was dried with magnesium sulfate (70g) after sequential washing with distilled water (100ml), 2N-sodium-hydroxide water solution (100ml), distilled water (100ml), and saturation brine (100ml). The title compound (63.8g, 87.8% of yield) of a white solid-state was obtained by carrying out reduced pressure drying after filtration and solvent distilling off.
1 H-NMR (300MHz, DMSO-d6) delta1.23-1.41 (5H, m), 1.67-1.78 (5H, m), 2.47 (1H, m), 4.43 (2H, s), 5.04 (1H, brs), 7.15 (2H, d, J= 8.0Hz), 7.21 (2H, d, J= 8.0Hz)
[0171] (2) 4-cyclohexyl benzaldehyde [0172]
[Formula 22]



[0173] Triethylamine (249ml, 1.79 mols) was added to the dimethyl sulfoxide (500ml) solution of 4-cyclohexyl benzyl alcohol (121.5g, 0.639 mols) obtained in the example 1 of manufacture (1). Under ice-cooling stirring, after adding gradually a pyridine sulfur-trioxide complex (163g, 1.02 mols), it stirred at the room temperature for 2 hours. Water (500ml) was dropped at reaction mixture under ice-cooling stirring. The mixed solvent (1:1) of n-hexane and ethyl acetate extracted, and it dried with the sodium sulfate after washing with saturation brine. The title compound (112g, 93.4% of yield) of colorless oily matter was obtained by carrying out reduced pressure drying after filtration and solvent distilling off.
1 H-NMR (300MHz, CDCl3) delta1.20-1.53 (5H, m), 1.72-1.95 (5H, m), 2.53-2.65 (1H, m), 5.04 (1H, brs), 7.37 (2H, d, J= 8.2Hz), 7.81 (2H, d, J= 8.2Hz), 9.97 (1H, s)
[0174] Example 14-(N-(4-(4-(N-(4-cyclohexyl benzyl)-N-methylamino) phenyl)-2-thiazolyl)-N-methylamino methyl) benzoic-acid (1)1-(4-methoxycarbonyl benzyl)-2-thiourea [0175]
[Formula 23]

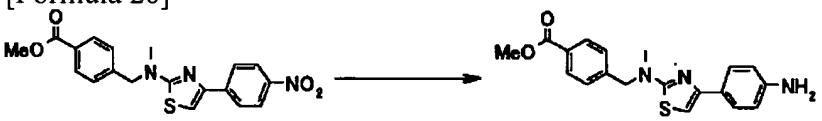
[0176] The bottom of an argon ambient atmosphere, 4-aminomethyl methyl benzoate 1 and 1'-thio carbonyldiimidazole (with a purity of 90% 166.0g, 0.843 mols) and triethylamine (123ml, 0.885 mols) were added to the chloroform (850ml, 5.0 v/w) suspension of a hydrochloride (170.0g, 0.843 mols) one by one. Aqueous ammonia (570ml, 8.43 mols) and a methanol (170ml, 1.0 v/w) were added 28% after 3-hour stirring at the room temperature, and it stirred all night. n-hexane (1700ml, 10.0 v/w) and water (850ml, 5.0 v/w) were added to reaction mixture one by one, and it stirred at the room temperature for 3 hours. The depositing crystal was filtered, with n-hexane (500ml) and water (500ml), after sequential washing, reduced pressure drying was carried out and the title compound (172.5g, 91.3% of yield) of a colorless solid-state was obtained.
1 H-NMR (300MHz, DMSO-d6) delta 3.84 (3H, s), 4.40 (1H, brs), 4.72 (2H, brs), 7.17 (1H, brs), 7.41 (2H, d, J= 8.1Hz), 7.93 (2H, d, J= 8.4Hz), 8.07 (1H, brs)
[0177] (2) 4-(4-(4-nitrophenyl)-2-thiazolyl) (aminomethyl) methyl benzoate [0178]
[Formula 24]



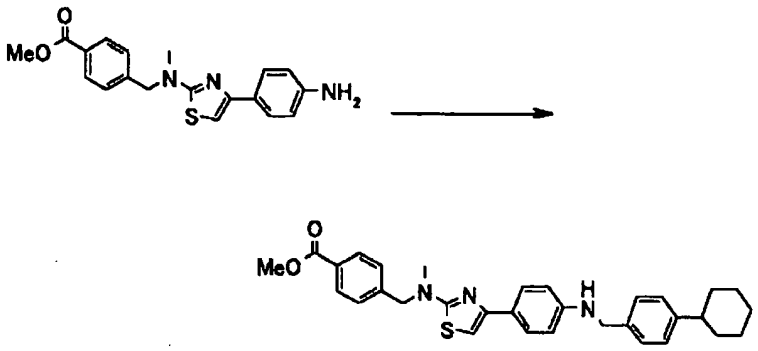
[0179] A 2-BUROMO-4'-nitro acetophenone (124.1g, 0.554 mols) and sodium bicarbonate (46.9g, 0.559 mols) were added to the acetonitrile (1380ml, 10.0 v/w) suspension of the 1-(4-methoxycarbonyl

benzyl)-2-thiourea (138.0g, 0.554 mols) obtained in the example 1 (1) one by one, and heating reflux was carried out for 2 hours. After cooling to a room temperature, water (1380ml, 10.0 v/w) and n-hexane (690ml, 5.0 v/w) were added one by one, and were stirred for 1 hour. The depositing crystal was filtered, by water (1000ml) and n-hexane (500ml), after sequential washing, reduced pressure drying was carried out and the title compound (183.9g, 89.9% of yield) of a yellow solid-state was obtained.
1 H-NMR (300MHz, DMSO-d6) delta 3.83 (3H, s), 4.63 (2H, d, J= 5.9Hz), 7.49 (1H, s), 7.54 (2H, d, J= 8.1Hz), 7.95 (2H, d, J= 8.1Hz), 8.06 (2H, d, J= 9.3Hz), 8.23 (2H, d, J= 6.0Hz), 8.43 (1H, t, J= 5.9Hz)
[0180] (3) 4-(N-methyl-N-(4-(4-nitrophenyl)-2-thiazolyl) aminomethyl) methyl benzoate [0181]
[Formula 25]

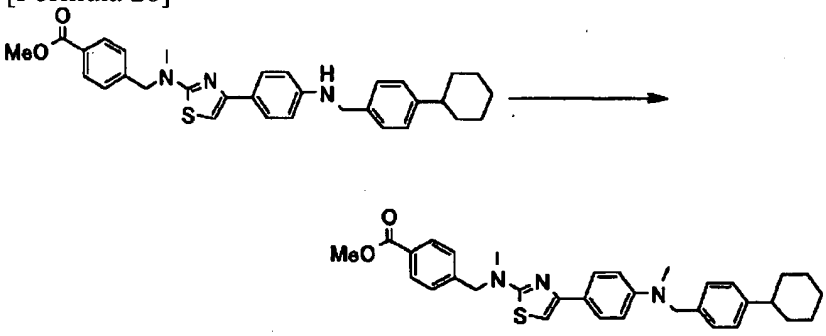
[0182] Under an argon ambient atmosphere, to the N.N-dimethylformamide (530ml, 2.5 v/w) suspension of sodium hydride (60% of contents, 26.4g, 0.661 mols) below 10 degrees C The N.N-dimethylformamide (743ml, 3.5 v/w) solution of 4-(4-(4-nitrophenyl)-2-thiazolyl) (aminomethyl) methyl benzoate (212.4g, 0.575 mols) obtained in the example 1 (2), The methyl iodide (41.2ml, 0.661 mols) was stirred at the room temperature after sequential dropping for 2 hours. Sodium hydride (60% of contents, 2.3g, 0.057 mols) was added, and it stirred at the room temperature for 1 hour. Below 10 degrees C, reaction mixture was dropped at water (2120ml, 10.0 v/w), and for 30 minutes, after stirring, diisopropyl ether (848ml, 4.0 v/w) was added, and it stirred at the room temperature for 2 hours. The depositing crystal was filtered, with diisopropyl ether (424ml) and water (424ml), after sequential washing, reduced pressure drying was carried out and the title compound (201.9g, 91.4% of yield) of a yellow solid-state was obtained.
1 H-NMR (300MHz, DMSO-d6) delta 3.14 (3H, s), 3.84 (3H, s), 4.87 (2H, s), 7.48 (2H, d, J= 8.3Hz), 7.61 (1H, s), 7.96 (2H, d, J= 8.3Hz), 8.11 (2H, d, J= 9.0Hz), 8.25 (2H, d, J= 9.0Hz)
[0183] (4) 4-(N-(4-(4-aminophenyl)-2-thiazolyl)-N-methylamino methyl) methyl benzoate [0184]
[Formula 26]



[0185] Palladium carbon (20.0g) was added to the ethanol (800ml, 4.0 v/w) and tetrahydrofuran (800ml, 4.0 v/w) mixing suspension of 4-(N-methyl-N-(4-(4-nitrophenyl)-2-thiazolyl) aminomethyl) methyl benzoate (200.0g, 0.522 mols) which were obtained in the example 1 (3) 10%, and it stirred with three atmospheric pressures under the hydrogen ambient atmosphere all night. Palladium carbon (20.0g) was added to filtrate 10% after cerite filtration, and reaction mixture was stirred with three atmospheric pressures under the hydrogen ambient atmosphere for 3 hours. Toluene (800ml) was added to residue after cerite filtration and solvent distilling off, the solvent was distilled off further, and the title compound (182.5g, 99.0% of yield) of a yellow solid-state was obtained.
1 H-NMR (300MHz, DMSO-d6) delta 3.07 (3H, s), 3.84 (3H, s), 4.82 (2H, s), 5.18 (2H, br), 6.54 (2H, d, J= 8.6Hz), 6.78 (1H, s), 7.45 (2H, d, J= 8.3Hz), 7.52 (2H, d, J= 8.5Hz), 7.95 (2H, d, J= 8.2Hz)
[0186] (5) 4-(N-(4-(4-(4-cyclohexyl benzylamino) phenyl)-2-thiazolyl)-N-methylamino methyl) methyl benzoate [0187]
[Formula 27]

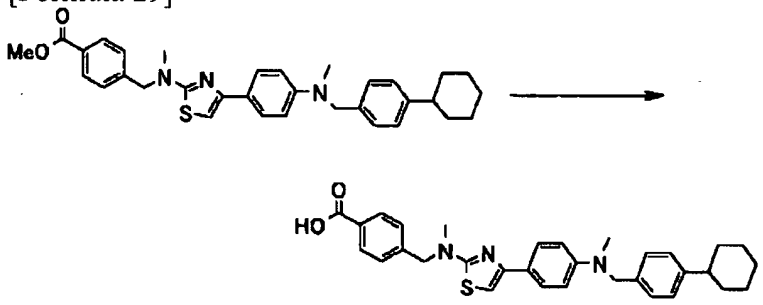


[0188] The tetrahydrofuran (1000ml, 5.7 v/w) was added to 4-(N-(4-(4-aminophenyl)-2-thiazolyl)-N-methylamino methyl) methyl benzoate (174.0g, 0.493 mols) obtained in the example 1 (4), and it was made to dissolve in it under an argon air current. The tetrahydrofuran (740ml, 4.3 v/w) solution of 4-cyclohexyl benzaldehyde (120.6g, 0.641 mols) obtained in the example 1 of manufacture (2) was poured in. The acetic acid (56.4ml, 0.986 mols) was added, and it stirred at the room temperature for 1 hour. The thoria SETOKISHI sodium borohydride (104.5g, 0.493 mols) was added under ice-cooling stirring, and it stirred at the room temperature for 1.5 hours. After ice-cooling, the acetic acid (28.2ml, 0.493 mols) and the thoria SETOKISHI sodium borohydride (52.2g, 0.246 mols) were added, and it stirred at the room temperature for 1.5 hours. It added to the saturation sodium-hydrogencarbonate water solution (2262ml, 13.0 v/w) carefully after ice-cooling reaction mixture. Ethyl acetate (522ml) extracts after 1-hour stirring at a room temperature, and they are distilled water (174ml) and saturation brine about an organic layer. (522ml) Sequential washing was carried out. It dried with magnesium sulfate (50.0g), the silica gel column chromatography (expansion solvent chloroform: ethyl-acetate =99.5:0.5) refined the obtained orange solid-state after solvent distilling off, and the title compound (80.3g, 31.0% of yield) of a light yellow solid-state was obtained.
1 H-NMR (300MHz, DMSO-d6) delta1.16-1.47 (5H, m), 1.65-1.80 (5H, m), 2.40-2.55 (1H, m), 3.60 (3H, s), 3.83 (3H, s), 4.22 (2H, d, J= 5.5Hz), 4.81 (2H, s), 6.32 (1H, t, J= 5.5Hz), 6.57 (1H, d, J= 8.7Hz), 6.77 (1H, s), 7.15 (2H, d, J= 8.1Hz), 7.26 (2H, d, J= 8.1Hz), 7.45 (2H, d, J= 8.3Hz), 7.53 (2H, d, J= 8.6Hz), 7.94 (2H, d, J= 8.3Hz)
[0189] (6) 4-(N-(4-(4-(N-(4-cyclohexyl benzyl)-N-methylamino) phenyl)-2-thiazolyl)-N-methylamino methyl) methyl benzoate [0190]
[Formula 28]

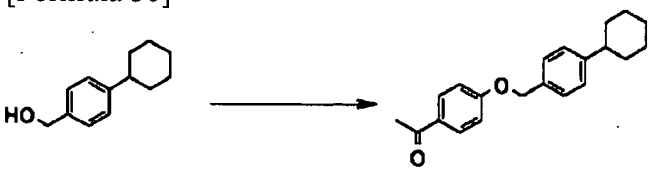


[0191] N,N-dimethylacetamide (351ml, 5.0 v/w) was added to 4-(N-(4-(4-(4-cyclohexyl benzylamino) phenyl)-2-thiazolyl)-N-methylamino methyl) methyl benzoate (70.3g, 0.134 mols) obtained in the example 1 (5) under the argon air current. Potassium carbonate (73.9g, 0.535 mols) was carefully added under stirring. The dimethyl sulfate (50.6ml, 0.535 mols) was added after 20-minute stirring at the room temperature. After 1-hour stirring, potassium carbonate (18.4g, 0.134 mols), and a dimethyl sulfate (12.7ml, 0.134 mols) were added at 50 degrees C, and it stirred at 60 degrees C for 2 hours. After cooling to a room temperature, n-hexane (422ml, 6.0 v/w) was added and it stirred for 1 hour. Distilled water (562ml, 8.0 v/w) was added after ice-cooling. The produced crystal was separated after room

temperature 1-hour stirring, and slurry washing was carried out with the methanol (352ml, 5.0 v/w). The tetrahydrofuran (180ml) was added to the obtained orange solid-state, filtrate was condensed after filtering insoluble matter, and the title compound (42.1g, 58.3% of yield) of a light yellow solid-state was obtained.
1 H-NMR (300MHz, DMSO-d6) delta1.16-1.47 (5H, m), 1.65-1.80 (5H, m), 2.40-2.55 (1H, m), 3.01 (3H, s), 3.07 (3H, s), 3.83 (3H, s), 4.54 (2H, s), 4.81 (2H, s), 6.71 (2H, d, J= 8.9Hz), 6.84 (1H, s), 7.08-7.16 (4H, m), 7.46 (2H, d, J= 8.3Hz), 7.62 (2H, d, J= 8.8Hz), 7.94 (2H, d, J= 8.3Hz)
[0192] (7) 4-(N-(4-(4-(N-(4-cyclohexyl benzyl)-N-methylamino) phenyl)-2-thiazolyl)-N-methylamino methyl) benzoic acid [0193]
[Formula 29]

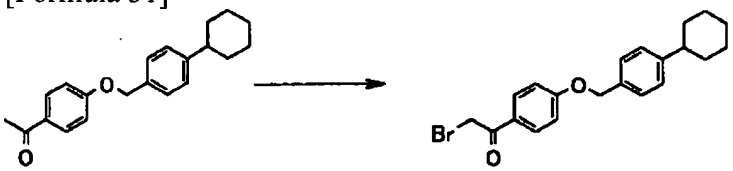


[0194] The tetrahydrofuran (202ml, 5.0 v/w) and the methanol (102ml, 3.0 v/w) were added to 4-(N-(4-(4-(N-(4-cyclohexyl benzyl)-N-methylamino) phenyl)-2-thiazolyl)-N-methylamino methyl) methyl benzoate (40.7g, 75.4mmol) obtained in the example 1 (6) under the argon air current. 1N-sodium-hydroxide water solution (151ml, 151mmol) was added under stirring at 50 degrees C. Distilled water (173ml, 4.25 v/w) was added after 1-hour stirring at 60 degrees C. 2N-hydrochloric acid (75.4ml, 151mmol) was carefully poured in under stirring. The produced crystal was separated after 1-hour stirring, sequential washing was carried out by distilled water (407ml) and ethanol (204ml), and the yellow solid-state (39.2g) was obtained by carrying out reduced pressure drying.
[0195] The tetrahydrofuran (172ml, 4.5 v/w) was added to the obtained yellow solid-state (38.2g), and it stirred at 50 degrees C for 1 hour. It washed by the tetrahydrofuran (19ml, 0.5 v/w) after filtration. Sequential impregnation of ethanol (134ml, 3.5 v/w) and distilled water (134ml, 3.5 v/w) was carried out under stirring at 50 degrees C at filtrate, and it stirred at stirring and a room temperature by 50 degrees C for 1 hour for 1 hour. The produced crystal was separated and the title compound (36.5g, 91.9% of yield) of a light yellow solid-state was obtained by carrying out reduced pressure drying after washing by ethanol (306ml).
1 H-NMR (300MHz, DMSO-d6) delta1.16-1.47 (5H, m), 1.65-1.80 (5H, m), 2.40-2.55 (1H, m), 3.01 (3H, s), 3.07 (3H, s), 4.54 (2H, s), 4.81 (2H, s), 6.71 (2H, d, J= 9.0Hz), 6.83 (1H, s), 7.08-7.16 (4H, m), 7.43 (2H, d, J= 8.4Hz), 7.63 (2H, d, J= 8.8Hz), 7.92 (2H, d, J= 8.2Hz), 12.85 (1H, brs)
Melting point 180 to 181 degree C [0196] Example 24-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino methyl) benzoic-acid potassium (1)4-(4-cyclohexyl benzyloxy) acetophenone [0197]
[Formula 30]

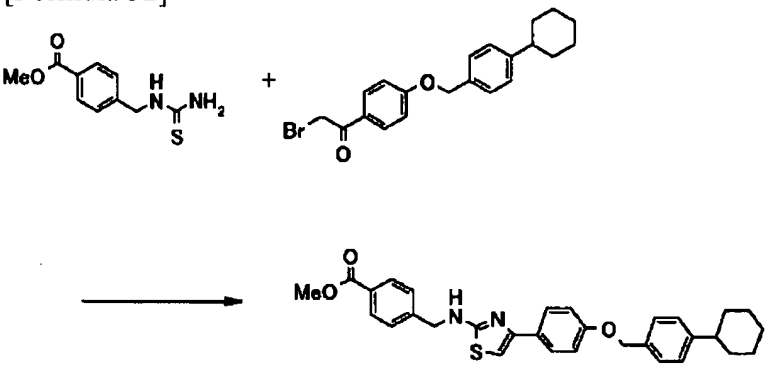


[0198] Toluene (225ml) and 48% hydrobromic acid (150ml) were added to 4-cyclohexyl benzyl alcohol (74.9g, 0.394 mols), and it stirred at 50 degrees C for 14 hours. Sequential washing of the organic layer was carried out after liquid separation with water (100ml), saturation sodium bicarbonate water (100ml), water (100ml), and saturation brine, and it dried with magnesium sulfate. Light yellow oily matter was

obtained by carrying out reduced pressure drying after filtration and solvent distilling off. The obtained oily matter was dissolved in N.N-dimethylformamide (500ml), a 4-hydroxy acetophenone (50.3g, 0.369 mols) and potassium carbonate (153g, 1.11 mols) were added, and it stirred for 70 minutes at 45 degrees C. Water (750ml) was dropped after ice-cooling, and it stirred for 30 minutes at the room temperature. The depositing crystal was filtered and rinsed, by n-hexane, after washing, it dried and the title compound (93.5g, 86.6% of yield) was obtained.
1 H-NMR (400MHz, DMSO-d6) delta1.15-1.52 (5H, m), 2.47 (1H, m) 1.58-1.87 (5H, m), 2.51 (3H, s), 5.15 (2H, s), 7.10 (2H, d, J= 9.3Hz), 7.24 (2H, d, J= 8.4Hz), 7.36 (2H, d, J= 8.4Hz), 7.92 (2H, d, J= 9.3Hz)
[0199] (2) 2'-BUROMO-4-(4-cyclohexyl benzyloxy) acetophenone [0200]
[Formula 31]

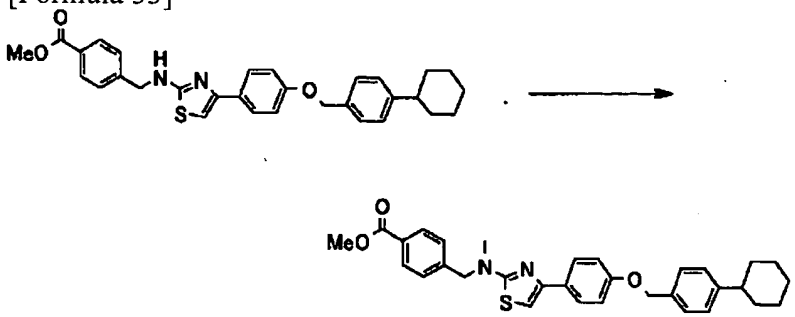


[0201] 1 of a bromine (10.5ml, 0.205 mols) and 2-dimethoxyethane (120ml) solution were dropped at 1 of 4-(4-cyclohexyl benzyloxy) acetophenone (60.0g, 0.195 mols) obtained in the example 2 (1), and 2-dimethoxyethane (480ml) suspension at the room temperature. Water (600ml) was dropped under ice-cooling after stirring for 90 minutes at the room temperature, and it stirred for 30 minutes at the room temperature. The depositing crystal was filtered and rinsed, by n-heptane, after washing, it dried and the title compound (68.2g, 90.1% of yield) was obtained.
1 H-NMR (400MHz, CDCl3) delta1.18-1.50 (5H, m), 2.51 (1H, m) 1.70-1.95 (5H, m), 4.38 (2H, s), 5.10 (2H, s), 7.03 (2H, d, J= 8.9Hz), 7.24 (2H, d, J= 8.4Hz), 7.34 (2H, d, J= 8.4Hz), 7.96 (2H, d, J= 8.9Hz)
[0202] (3) 4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl aminomethyl) methyl benzoate [0203]
[Formula 32]



[0204] The acetonitrile (630ml) was added to the 2'-BUROMO-4-(4-cyclohexyl benzyloxy) acetophenone (62.7g, 0.162 mols) and sodium bicarbonate (13.6g, 0.162 mols) which were obtained in the 1-(4-methoxycarbonyl benzyl)-2-thiourea (33.0g, 0.147 mols) obtained in the example 1 (1), and the example 2 (2), and heating reflux was carried out for 4 hours. After cooling to a room temperature, water (630ml) was added and it stirred at this temperature for 1 hour. The depositing crystal was filtered, it dried after sequential washing 50% with an acetonitrile (130ml), water (2L), and diisopropyl ether (500ml), and the title compound (quantitive 76.4g) was obtained.
1 H-NMR (400MHz, DMSO-d6) delta1.16-1.47 (5H, m), 2.50 (1H, m) 1.65-1.80 (5H, m), 3.84 (3H, s), 4.61 (2H, brs), 5.06 (2H, s), 6.91 (1H, s), 7.00 (2H, d, J= 8.9Hz) 7.23 (2H, d, J= 8.1Hz), 7.35 (2H, d, J= 8.1Hz), 7.53 (2H, d, J= 8.1Hz), 7.70 (2H, d, J= 8.9Hz), 7.94 (2H, d, J= 8.1Hz), 8.28-8.52 (1H, brs)
[0205] (4) 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino methyl) methyl benzoate [0206]

[Formula 33]

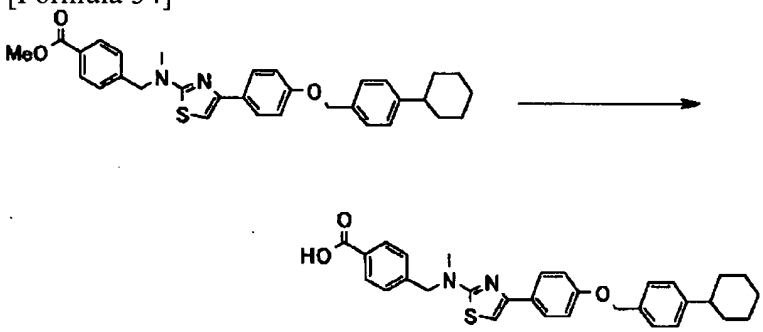


[0207] The N.N-dimethylformamide (130ml) suspension of 4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl aminomethyl) methyl benzoate (65.0g, 0.127 mols) obtained in the example 2 (3) below 10 degrees C and a dimethyl sulfate (15.0ml, 0.159 mols) were stirred at the room temperature after sequential dropping under the argon ambient atmosphere for 1 hour to the N.N-dimethylformamide (130ml) suspension of sodium hydride (60% of contents, 6.09g, 0.152 mols). Below 10 degrees C, sequential dropping of diisopropyl ether (195ml) and the water (130ml) was carried out, and it stirred for 30 minutes at the room temperature. The depositing crystal was filtered, with diisopropyl ether (195ml) and water (130ml), after sequential washing, it dried and the title compound (56.0g, 83.7%) was obtained.

1 H-NMR (400MHz, DMSO-d6) delta1.16-1.47 (5H, m), 2.50 (1H, m) 1.65-1.86 (5H, m), 3.09 (3H, s), 3.84 (3H, s), 4.83 (2H, s), 5.06 (2H, s), 7.00 (2H, d, J= 8.9Hz), 7.01 (1H, s), 7.23 (2H, d, J= 8.1Hz), 7.35 (2H, d, J= 8.1Hz), 7.46 (2H, d, J= 8.1Hz), 7.76 (2H, d, J= 8.9Hz), 7.94 (2H, d, J= 8.1Hz)

[0208] (5) 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino methyl) benzoic acid [0209]

[Formula 34]

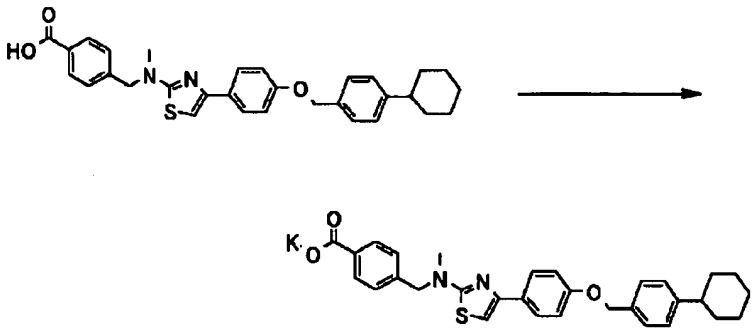


[0210] The tetrahydrofuran (250ml), the methanol (250ml), and 2N-sodium-hydroxide water solution (95.0ml, 190mmol) were added to 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino methyl) methyl benzoate (50.0g, 94.9mmol) obtained in the example 2 (4), and heating reflux was carried out for 40 minutes under the argon ambient atmosphere. Water (310ml) was added to reaction mixture, 2N-hydrochloric acid (95.0ml, 190mmol) was dropped after cooling to a room temperature, and it stirred for 90 minutes. The produced crystal was separated and the title compound (48.5g, 99.7% of yield) was obtained by drying after washing with water (700mL).

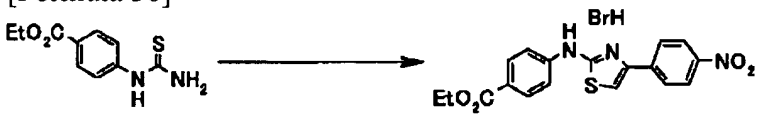
1 H-NMR (400MHz, DMSO-d6) delta1.15-1.47 (5H, m), 2.47 (1H, m) 1.64-1.85 (5H, m), 3.09 (3H, s), 4.82 (2H, s), 5.06 (2H, s), 7.00 (2H, d, J= 9.2Hz), 7.02 (1H, s), 7.23 (2H, d, J= 8.4Hz), 7.35 (2H, d, J= 8.4Hz), 7.42 (2H, d, J= 8.1Hz), 7.77 (2H, d, J= 9.2Hz), 7.92 (2H, d, J= 8.1Hz)

[0211] (6) 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino methyl) benzoic-acid potassium [0212]

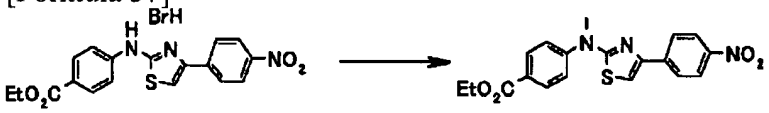
[Formula 35]



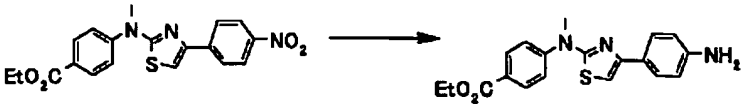
[0213] Under the argon ambient atmosphere, after adding 1N-potassium-hydroxide water solution (56.0ml) to the suspension of 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino methyl) benzoic acid (30.0g, 58.5mmol) obtained in the example 2 (5) at 50 degrees C, heating reflux was carried out for 40 minutes. It stirred for 45 minutes at the room temperature, the crystal was separated, and the title compound (28.0g, 90.9% of yield) was obtained by drying after washing by the tetrahydrofuran-ethanol mixed solvent (3:1,150ml) and ethanol (210ml).
1 H-NMR (400MHz, DMSO-d6) delta1.17-1.47 (5H, m), 2.50 (1H, m) 1.65-1.84 (5H, m), 3.04 (3H, s), 4.71 (2H, s), 5.07 (2H, s), 6.99 (1H, s), 7.00 (2H, d, J= 8.9Hz), 7.19 (2H, d, J= 8.1Hz), 7.23 (2H, d, J= 8.1Hz), 7.36 (2H, d, J= 8.1Hz), 7.77 (2H, d, J= 8.9Hz), 7.79 (2H, d, J= 8.1Hz)
Melting point 288 to 291 degree C (decomposition)
[0214] Example 34-(N-(4-(4-(4-cyclohexyl benzylamino) phenyl)-2-thiazolyl)-N-methylamino) benzoic-acid (1)4-(4-(4-nitrophenyl)-2-thiazolyl) (amino) ethyl benzoate Hydrobromate [0215]
[Formula 36]



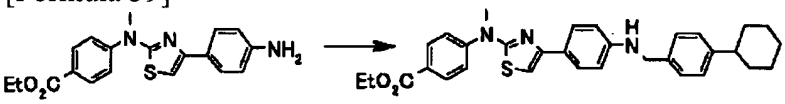
The heating reflux of a 2'-BUROMO-4-nitro acetophenone (87.1g, 0.357 mols) and the acetonitrile (1.6L) solution of 1-(4-ethoxycarbonyl phenyl)-2-thiourea (80.0g, 0.357 mols) was carried out under the argon ambient atmosphere for 1 hour. After cooling to a room temperature, the generated crystal was separated, it dried, and the title compound (153g, 94.9% of yield) was obtained.
1 H-NMR (400MHz, DMSO-d6) delta 1.33 (3H, t, J= 7.1Hz), 4.29 (2H, q, J= 7.1Hz), 7.84 (1H, s), 7.87 (2H, d, J= 9.1Hz), 7.97 (2H, d, J= 8.6Hz), 8.22 (2H, d, J= 8.6Hz), 8.27 (2H, d, J= 9.2Hz), 10.82 (1H, s)
[0216] (2) 4-(N-methyl-N-(4-(4-nitrophenyl)-2-thiazolyl) amino) ethyl benzoate [0217]
[Formula 37]



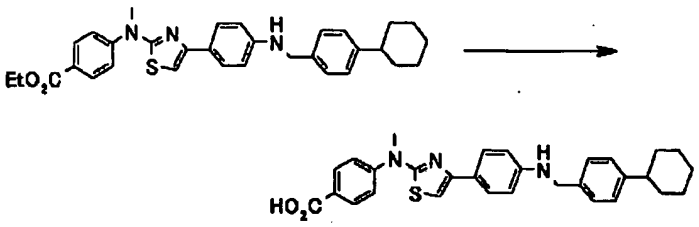
[0218] 4-(4-(4-nitrophenyl)-2-thiazolyl) (amino) ethyl benzoate obtained in the example 3 (1) under the nitrogen air current N.N-dimethylformamide (1.05L, 7.0 v/w) was added to the hydrobromate (150g, 0.333 mols). Potassium carbonate (138g, 0.999 mols) was carefully added under ice-cooling stirring. The dimethyl sulfate (63.2ml, 0.666 mols) was added after 20-minute stirring at the room temperature. Distilled water (1.05L, 7.0 v/w) was added under ice-cooling stirring after 2-hour stirring at 60 degrees C. The produced crystal was separated after 1-hour stirring under ice-cooling, and the title compound (127g, 99.3% of yield) of an orange crystal was obtained by carrying out reduced pressure drying after washing with distilled water (450mL).
1 H-NMR (400MHz, DMSO-d6) delta 1.34 (3H, t, J= 7.1Hz), 3.62 (3H, s), 4.33 (2H, q, J= 7.1Hz), 7.74 (2H, d, J= 8.8Hz), 7.78 (1H, s), 8.03 (2H, d, J= 8.8Hz), 8.14 (2H, d, J= 9.0Hz), 8.28 (2H, d, J= 9.0Hz)
[0219] (3) 4-(N-(4-(4-aminophenyl)-2-thiazolyl)-N-methylamino) ethyl benzoate [0220]
[Formula 38]



[0221] N.N-dimethylformamide (1.20L, 10.0 v/w) was added to 4-(N-methyl-N-(4-(4-nitrophenyl)-2-thiazolyl) amino) ethyl benzoate (123g, 0.321 mols) obtained in the example 3 (2) under the nitrogen air current. Sodium dithionite (80%purity, 210g, 0.963 mols) was added under room temperature stirring. Distilled water (123ml, 1.0 v/w) was carefully added after 10-minute stirring at the room temperature. At 100 degrees C, triethylamine (223ml, 1.61 mols) was added at 80 degrees C after 1.5-hour stirring, and water cooling was carried out to the room temperature. Distilled water (1.1L, 9.0 v/w) was added after 1-hour stirring at the room temperature. Double sampling was carried out with ethyl acetate (1.20L) after 30-minute stirring at the room temperature, and the organic layer was dried with magnesium sulfate (60g) after sequential washing with distilled water (400ml) and saturation brine (400ml). The title compound (67.0g, 63.0% of yield) of an orange solid-state was obtained from yellow by filtration, solvent distilling off, toluene azeotropy, and carrying out reduced pressure drying.
1 H-NMR (400MHz, DMSO-d6) delta 1.33 (3H, t, J= 7.0Hz), 3.57 (3H, s), 4.32 (2H, q, J= 7.0Hz), 5.27 (2H, brs), 6.59 (2H, d, J= 8.6Hz), 7.02 (1H, s), 7.56 (2H, d, J= 8.6Hz), 7.71 (2H, d, J= 9.0Hz), 7.99 (2H, d, J= 9.0Hz)
[0222] (4) 4-(N-(4-(4-(4-cyclohexyl benzylamino) phenyl)-2-thiazolyl)-N-methylamino) ethyl benzoate
[0223]
[Formula 39]



[0224] The tetrahydrofuran (306ml, 6.0 v/w) was added to 4-(N-(4-(4-aminophenyl)-2-thiazolyl)-N-methylamino) ethyl benzoate (51.0g, 0.144 mols) obtained in the example 3 (3) under the nitrogen air current. The tetrahydrofuran (153ml, 3.0 v/w) solution of 4-cyclohexyl benzaldehyde (30.0g, 0.158 mols) obtained in the example 1 of manufacture (2) was poured in under room temperature stirring. After washing and being crowded with a tetrahydrofuran (51ml, 1.0 v/w), it stirred at the room temperature for 30 minutes. The thoria SETOKISHI sodium borohydride (46.0g, 0.216 mols) and the acetic acid (12.4ml, 0.216 mols) were added under ice-cooling stirring, and it stirred at the room temperature for 1.5 hours. Saturation sodium-hydrogencarbonate water (510ml, 10.0 v/w) was carefully added under ice-cooling stirring. Ethyl acetate (408ml) extracted after 1-hour stirring at the room temperature, and the organic layer was dried with magnesium sulfate (50g) after sequential washing with distilled water (255ml) and saturation brine (255ml). Isopropyl alcohol (510ml, 10.0 v/w) was added to the obtained orange solid-state after filtration and solvent distilling off, and it stirred at 60 degrees C for 1 hour. The produced crystal was separated after 1-hour stirring under ice-cooling, and the title compound (58.0g, 77.0% of yield) of a light yellow solid-state was obtained by carrying out reduced pressure drying after washing with isopropyl alcohol (102ml) and tert-butyl methyl ether (102ml).
1 H-NMR (400MHz, DMSO-d6) delta1.23-1.40 (8H, m), 2.46 (1H, s) 1.67-1.78 (5H, m), 3.56 (3H, s), 4.24 (2H, d, J= 6.1Hz) 4.31 (2H, q, J= 7.1Hz), 6.35 (1H, t, J= 6.1Hz) 6.60 (2H, d, J= 8.6Hz), 7.01 (1H, s), 7.16 (2H, d, J= 7.6Hz), 7.27 (6H, d, J= 7.6Hz), 7.57 (2H, d, J= 8.6Hz), 7.70 (2H, d, J= 8.9Hz), 7.98 (2H, d, J= 8.9Hz)
[0225] (5) 4-(N-(4-(4-(4-cyclohexyl benzylamino) phenyl)-2-thiazolyl)-N-methylamino) benzoic acid
[0226]
[Formula 40]



[0227] The tetrahydrofuran (312ml, 6.0 v/w) and the methanol (104ml, 2.0 v/w) were added to 4-(N-(4-(4-(4-cyclohexyl benzylamino) phenyl)-2-thiazolyl)-N-methylamino) ethyl benzoate (52.0g, 98.9mmol) obtained in the example 3 (4) under the nitrogen air current. 2N-sodium-hydroxide water solution (98.9ml, 197.8mmol) was added under ice-cooling stirring. Distilled water (104ml, 2.0 v/w) was added after 2-hour stirring at 60 degrees C. 2N-hydrochloric acid (98.9ml, 197.8mmol) was carefully poured in under ice-cooling stirring. The yellow solid-state (51.9g) was obtained by separating the produced crystal after 1-hour stirring under ice-cooling, and carrying out reduced pressure drying after washing with distilled water (156ml). The tetrahydrofuran (750ml, 15.0 v/w) was added to 50.0g of obtained yellow solid-states, and it stirred at 60 degrees C for 1 hour. Precipitate after radiationnal cooling was carried out the ** exception to the room temperature, and it washed by the tetrahydrofuran (100ml, 2.0 v/w). Sequential impregnation of ethanol (150ml) and distilled water (150ml) was carried out under room temperature stirring at filtrate. The produced crystal was separated after 1-hour stirring under ice-cooling, and the rough title compound (33.6g) of a yellow solid-state was obtained by carrying out reduced pressure drying after sequential washing with distilled water (200ml) and 50% ethanol water (200ml). Ethanol (350ml, 7.0 v/w) was added and it stirred at the room temperature for 2 hours. The produced crystal was separated and the title compound (32.1g, 64.2% of yield) of a light yellow solid-state was obtained by carrying out reduced pressure drying after washing by ethanol (200ml).
1 H-NMR (400MHz, DMSO-d6) delta 1.20-1.40 (5H, m), 2.43 (1H, m) 1.67-1.78 (5H, m), 3.56 (1H, s), 4.23 (3H, d, J= 5.1Hz) 6.34 (1H, brt, J= 5.1Hz), 6.60 (2H, d, J= 8.6Hz), 6.98 (1H, s), 7.16 (2H, d, J= 8.1Hz), 7.27 (2H, d, J= 8.1Hz), 7.57 (2H, d, J= 8.6Hz), 7.67 (2H, d, J= 8.9Hz), 7.97 (2H, d, J= 8.9Hz)
Melting point 252 to 253 degree C (decomposition)
[0228] By the same approach as examples 1-3, the following compound was further manufactured by in addition to this using a conventional method again if needed.
[0229] 4-(4-(4-benzoyl aminophenyl)-2-thiazolyl amino) benzoic acid (example 4), 4-(4-(4-(4-tert-butyl benzoylamino) phenyl)-2-thiazolyl amino) benzoic acid (example 5), 4-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl amino) benzoic acid (example 6), 4-(N-(4-(4-benzoyl aminophenyl)-2-thiazolyl)-N-ethylamino) benzoic acid (example 7), 4-(N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-N-ethylamino) benzoic acid (example 8), 4-(N-(4-(4-benzoyl aminophenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid (example 9), 4-(N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid (example 10), [0230] 4-(N-(4-(4-(cyclohexane carbonylamino) phenyl)-2-thiazolyl)-N-ethylamino) benzoic acid (example 11), 4-(N-(4-(4-(cyclohexane carbonylamino) phenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid (example 12), 4-(N-(4-(4-(cyclohexane carbonylamino) phenyl)-2-thiazolyl)-N-isobutyl amino) benzoic acid (example 13), 4-(N-carboxymethyl-N-(4-(4-(cyclohexane carbonylamino) phenyl)-2-thiazolyl) amino) benzoic acid (example 14), 4-(N-(4-(4-benzoyl aminophenyl)-2-thiazolyl)-N-isobutyl amino) benzoic acid (example 15), 4-(N-(4-(4-benzoyl aminophenyl)-2-thiazolyl)-N-carboxy methylamino) benzoic acid (example 16), 4-(N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-N-isobutyl amino) benzoic acid (example 17), 4-(N-carboxymethyl-N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl) amino) benzoic acid (example 18), 4-(N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-N-methylamino) benzoic acid (example 19), 4-(N-(4-(4-(4-tert-butyl benzoylamino) phenyl)-2-thiazolyl)-N-methylamino) benzoic acid (example 20), [0231] 4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl amino) benzoic acid (example 21), 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino) benzoic acid (example 22), 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-ethylamino) benzoic acid (example 23), 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-

isopropylamino) benzoic acid (example 24), 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-cyclohexyl methylamino) benzoic acid (example 25), 4-(N-(3-carboxy propyl)-N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl) amino) benzoic acid (example 26), 3-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl amino) benzoic acid (example 27), 3-(N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid (example 28), 4-(N-isopropyl-N-(4-(4-(4-morpholino benzoylamino) phenyl)-2-thiazolyl) amino) benzoic acid Hydrochloride (example 29), 3-(N-isopropyl-N-(4-(4-(4-piperidino benzoylamino) phenyl)-2-thiazolyl) amino) benzoic acid A hydrochloride (example 30), [0232] 3-(N-isopropyl-N-(4-(4-(4-morpholino benzoylamino) phenyl)-2-thiazolyl) amino) benzoic acid Hydrochloride (example 31), 4-(N-isopropyl-N-(4-(4-(4-piperidino benzoylamino) phenyl)-2-thiazolyl) amino) benzoic acid Hydrochloride (example 32), 4-(N-isopropyl-N-(4-(4-(4-(4-methyl piperidino) benzoylamino) phenyl)-2-thiazolyl) amino) benzoic acid Hydrochloride (example 33), 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-isopropylamino) sodium benzoate (example 34), 4-(N-(4-(4-(4-(3, 5-dimethyl piperidino) benzoylamino) phenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid Hydrochloride (example 35), cis-4-(N-(4-(4-(4-(2, 6-dimethyl morpholino) benzoylamino) phenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid Hydrochloride (example 36), 4-(N-isopropyl-N-(4-(4-(4-(4-methyl-1-piperazinyl) benzoylamino) phenyl)-2-thiazolyl) amino) sodium benzoate (example 37), A 2-chloro-4-(N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid (example 38), 2-chloro-4-(N-isopropyl-N-(4-(4-(4-piperidino benzoylamino) phenyl)-2-thiazolyl) amino) benzoic-acid hydrochloride (fruit) Example of ** 39, 2-chloro-4-(N-isopropyl-N-(4-(4-(4-morpholino benzoylamino) phenyl)-2-thiazolyl) amino) benzoic acid A hydrochloride (example 40), [0233] A 2-chloro-4-(N-isopropyl-N-(4-(4-(4-(4-methyl-1-piperazinyl) benzoylamino) phenyl)-2-thiazolyl) amino) benzoic acid (example 41), 4-(1-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-1-methylethyl) benzoic acid (example 42), 4-(1-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-1-methylethyl) benzoic acid (example 43), 4-(1-methyl-1-(4-(4-(4-morpholino benzoylamino) phenyl)-2-thiazolyl) ethyl) benzoic acid (example 44), 4-(1-methyl-1-(4-(4-(4-piperidino benzoylamino) phenyl)-2-thiazolyl) ethyl) benzoic acid (example 45), 4-(N-(4-(4-(4-cyclohexyl butyryl amino) phenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid (example 46), 4-(4-(4-(4-tert-butyl benzyloxy) phenyl)-2-thiazolyl methyl) benzoic acid (example 47), 4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl methyl) benzoic acid (example 48), 4-(4-(4-(4-carboxy benzyloxy) phenyl)-2-thiazolyl methyl) benzoic acid (example 49), (4-(N-(4-(4-(cyclohexane carbonylamino) phenyl)-2-thiazolyl)-N-isopropylamino) phenoxy) An acetic acid (example 50), [0234] An acetic acid (example 51), (4-(N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-N-isopropylamino) phenoxy) 4-(N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-N-isopropylamino)-2, 3 and 5, 6-tetrafluoro benzoic acid (example 52), An acetic acid (example 53), (4-(N-isopropyl-N-(4-(4-(4-piperidino benzoylamino) phenyl)-2-thiazolyl) amino) phenoxy) An acetic acid (example 54), (4-(N-isopropyl-N-(4-(4-(4-morpholino benzoylamino) phenyl)-2-thiazolyl) amino) phenoxy) An acetic acid (example 55), (4-(N-(4-(4-(3, 5-screw (trifluoromethyl) benzoylamino) phenyl)-2-thiazolyl)-N-isopropylamino) phenoxy) An acetic acid (example 56), (4-(N-(4-(4-(3, 5-dichloro benzoylamino) phenyl)-2-thiazolyl)-N-isopropylamino) phenoxy) An acetic acid (example 57), (4-(N-isopropyl-N-(4-(4-(2-piperidino-5-pyridine carbonylamino) phenyl)-2-thiazolyl) amino) phenoxy) 4-(N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-N-cyclohexyl methylamino) benzoic acid (example 58), 4-(N-cyclohexyl methyl-N-(4-(4-(4-trifluoromethyl benzoylamino) phenyl)-2-thiazolyl) amino) benzoic acid (example 59), 4-(N-(4-(4-(N-(4-cyclohexyl benzoyl)-N-methylamino) phenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid (example 60), [0235] 4-(N-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 61), 4-(N-isopropyl-N-(4-(4-(4-piperidino benzoylamino) phenyl)-2-thiazolyl) amino) (methyl) benzoic acid (example 62), 4-(N-isopropyl-N-(4-(4-(4-morpholino benzoylamino) phenyl)-2-thiazolyl) amino) (methyl) benzoic acid (example 63), 4-(N-(4-(4-(4-biphenyl carbonylamino) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 64), 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 65), 4-(2-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl) ethyl) benzoic acid (example 66), 4-(N-(4-(4-(4-cyclohexyl

benzylamino) phenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid (example 67), 4-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl methyl) benzoic acid (example 68), 4-(4-(4-(4-isopropoxy benzoylamino) phenyl)-2-thiazolyl methyl) benzoic acid (example 69), 4-(4-(4-(4-(1-pyrrolyl) benzoylamino) phenyl)-2-thiazolyl methyl) benzoic acid (example 70), [0236] 4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazole carbonyl) benzoic acid (example 71), A 4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl amino)-3-(2-cyclohexyl ethoxy) benzoic acid (example 72), A 3-benzyloxy-4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl amino) benzoic acid (example 73), 3-(4-carboxy benzyloxy)-4 - (4- (4-(4-cyclohexyl benzyloxy) FU)) An ENIRU-2-thiazolyl amino benzoic acid (example 74), a 4-cyclohexyl-N-(4-(2-(N-isopropyl-N-(4-(1H-tetrazole-5-IRU) phenyl) amino)-4-thiazolyl) phenyl) benzamide (example 75), 3-(2-(4-(4-(4-cyclohexyl benzoylamino) phenyl)-2-thiazolyl) ethyl) benzoic acid (example 76), 4-(N-(4-(4-(3, 4-dichloro benzyloxy) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 77), An N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-isopropyl-(4-(1H-tetrazole-5-IRU) phenyl) amine (example 78), An N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-isopropyl-(4-(1H-tetrazole-5-IRU) benzyl) amine (example 79), An N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-isopropyl-(3-(1H-tetrazole-5-IRU) benzyl) amine (example 80), [0237] 4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl amino) (methyl) benzoic acid (example 81), 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino) (methyl) benzoic acid (example 82), 4-(N-(4-(4-(4-(4-fluoro phenyl)-2-methyl-5-thiazolyl methoxy) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 83), 4-(N-(4-(4-(4'-chloro-4-methoxy biphenyl-2-ylmethoxy) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 84), 4-(N-isopropyl-N-(4-(4-(4-methyl-2-(4-trifluoro methylphenyl)-5-thiazolyl methoxy) phenyl)-2-thiazolyl) amino) (methyl) benzoic acid (example 85), An N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-isopropyl-(2-(1H-tetrazole-5-IRU) benzyl) amine (example 86), 3-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 87), 2-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 88), 4-(N-(4-(4-(3, 4-dichloro benzyloxy) phenyl)-2-thiazolyl)-N-methylamino) benzoic acid (example 89), 4-(1-(4-(4-(3, 4-dichloro benzyloxy) phenyl)-2-thiazolyl)-1-methylethyl) benzoic acid (example 90), [0238] 4-(1-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl) cyclopentyl) benzoic acid (example 91), 4-(1-(4-(4-(4-biphenylyl methoxy) phenyl)-2-thiazolyl)-1-methylethyl) benzoic acid (example 92), 4-(1-(4-(4-(3, 4-dichloro benzyloxy) phenyl)-2-thiazolyl) cyclohexyl) benzoic acid (example 93), 4-(4-(4-(3, 4-dichloro benzyloxy) phenyl)-2-thiazolyl amino) benzoic acid (example 94), 4-(4-(4-(4-biphenylyl methoxy) phenyl)-2-thiazolyl amino) benzoic acid (example 95), 4-(N-(4-(4-(3, 4-dichloro benzyloxy) phenyl)-2-thiazolyl)-N-isopropylamino) benzoic acid (example 96), 4-(N-(4-(4-(3, 4-dichloro benzyloxy) phenyl)-2-thiazolyl)-N-(2-dimethylaminoethyl) amino) benzoic acid (example 97), 4-(N-(4-(4-(3, 4-dichloro benzyloxy) phenyl)-2-thiazolyl)-N-(2-piperidino ethyl) amino) benzoic acid (example 98), 4-(N-(4-(4-(3, 4-dichloro benzyloxy) phenyl)-2-thiazolyl)-N-(2-methoxy ethyl) amino) benzoic acid (example 99), 4-(1-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl) cyclohexyl) benzoic acid (example 100), [0239] 4-(4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl) tetrahydropyran-4-IRU) benzoic acid (example 101), 4-(N-(4-(4-(N-(4-cyclohexyl benzyl)-N-methylamino) phenyl)-2-thiazolyl)-N-methylamino methyl) sodium benzoate (example 102), 4-(N-isopropyl-N-(4-(4-(4-trifluoromethyl benzyloxy) phenyl)-2-thiazolyl) amino) (methyl) benzoic acid (example 103), 4-(N-(4-(4-(4-tert-butylbenzene sulfonylamino) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 104), 4-(N-(4-(4-(3, 4-dichlorobenzene sulfonylamino) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 105), 4-(N-isopropyl-N-(4-(4-(4-trifluoromethyl benzenesulphonyl amino) phenyl)-2-thiazolyl) amino) (methyl) benzoic acid (example 106), 4 - (N- (4-(4-(4-cyclohexylbenzene sulfonylamino) phenyl)-2-CHIAZO)) A Lil-N-isopropylamino methyl benzoic acid (example 107), 4-(N-(4-(4-(4-cyclohexyl benzyl sulfanil) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 108), 4-(N-(4-(4-dibenzyl aminophenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 109), 4-(N-(4-(4-(N-(4-cyclohexyl benzenesulphonyl)-N-methylamino) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 110), [0240] 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-

propylamino) (methyl) benzoic acid (example 111), 4-(N-(4-(4-(4-cyclohexyl phenylmethane sulfonyl) phenyl)-2-thiazolyl)-N-isopropylamino) (methyl) benzoic acid (example 112), 4-(N-benzyl-N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl) amino) (methyl) benzoic acid (example 113), 4-(N-(4-(4-(N-benzyl-N-(4-cyclohexyl benzyl) amino) phenyl)-2-thiazolyl)-N-methylamino) (methyl) benzoic acid (example 114), 4-(N-(4-(4-(4-cyclohexyl benzylamino) phenyl)-2-thiazolyl)-N-methylamino) (methyl) benzoic acid (example 115), 4-(N-cyclohexyl methyl-N-(4-(4-(3, 4-dichloro benzylamino) phenyl)-2-thiazolyl) amino) (methyl) benzoic acid (example 116), 4-(N-(4-(4-(screw (3, 4-dichloro benzyl) amino) phenyl)-2-thiazolyl)-N-cyclohexyl methylamino) (methyl) benzoic acid (example 117), 4-(N-cyclohexyl methyl-N-(4-(4-(N-(3, 4-dichloro benzyl)-N-methylamino) phenyl)-2-thiazolyl) amino) (methyl) benzoic acid (example 118), 4-(N-(4-(4-(N-allyl compound-N-(4-cyclohexyl benzyl) amino) phenyl)-2-thiazolyl)-N-methylamino) (methyl) benzoic acid (example 119), 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino) (methyl) sodium benzoate (example 120), [0241] 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino) (methyl) benzoic acid N-methyl-D-glucamine salt (example 121), 4-(N-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazolyl)-N-methylamino) (methyl) benzoic acid Tris (hydroxymethyl) aminomethane salt (example 122), 4-(N-(4-(4-(N-benzyl-N-cyclohexyl methylamino) phenyl)-2-thiazolyl)-N-methylamino) (methyl) benzoic acid (example 123), 4-(N-(4-(4-(N-cyclohexyl methyl-N-(4-trifluoro methylbenzyl) amino) phenyl)-2-thiazolyl)-N-methylamino) (methyl) benzoic acid (example 124), 4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazole carbonyl) sodium benzoate (example 125), 4-(4-(4-(4-cyclohexyl benzyloxy) phenyl)-2-thiazole carbonyl) benzoic-acid potassium (example 126), 4-(N-isopropyl-N-(4-(4-(3-piperidino benzyloxy) phenyl)-2-thiazolyl) amino) (methyl) benzoic acid Dihydrochloride (example 127), 4-(N-(4-(4-(3, 4-dichloro benzylamino) phenyl)-2-thiazolyl)-N-methylamino) benzoic acid (example 128), 4-(N-cyclohexyl methyl-N-(4-(4-(3, 4-dichloro benzylamino) phenyl)-2-thiazolyl) amino) benzoic acid (example 129), 4-(N-cyclohexyl methyl-N-(4-(4-(4-isopropyl benzylamino) phenyl)-2-thiazolyl) amino) benzoic acid (example 130), [0242] 4-(N-cyclohexyl methyl-N-(4-(4-(4-isobutyl benzylamino) phenyl)-2-thiazolyl) amino) benzoic acid (example 131), 4-(N-(4-(4-(N-(4-cyclohexyl benzyl)-N-methylamino) phenyl)-2-thiazolyl)-N-methylamino) benzoic acid (example 132), 4-(N-methyl-N-(4-(4-(4-trifluoromethyl benzylamino) phenyl)-2-thiazolyl) amino) benzoic acid (example 133), 4-(N-cyclohexyl methyl-N-(4-(4-(4-trifluoromethyl benzylamino) phenyl)-2-thiazolyl) amino) benzoic acid (example 134),

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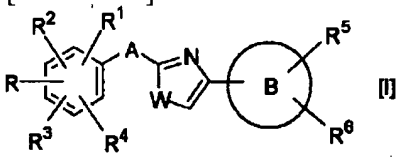
Since it became timeout time, translation result display processing is stopped.

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] General formula [I]
[Formula 1]



[I]

W shows a sulfur atom or an oxygen atom among [type, and;R is (1)-COOR7 (among a formula). R7 is (2)-X1-A1-COOR7 (among a formula) which shows a hydrogen atom or a low-grade alkyl group. X1 is -O-, -N(R15)-, or -S(O) p. - (R15 shows a hydrogen atom or a low-grade alkyl group among a formula) (3) tetrazolyl groups are shown. p -- 0, 1, or 2 -- being shown -- or it is shown, A1 shows a low-grade alkylene group and R7 shows a hydrogen atom or a low-grade alkyl group, R1, R2, R3, and R4 Independently, respectively (1) hydrogen atom, (2) halogen atom, (3) hydroxyl groups, (4) The low-grade cycloalkyl alkyloxy radical which may be permuted, the aralkyloxy radical by which (5) permutations may be carried out, (6) A cyano group, (7) nitro groups, (8) low-grade alkyl group, (9) low-grade halo alkyl group, (10) A lower alkoxy group or (11) low-grade haloalkoxy radical is shown, and;A is -(CH2) m-X. - (among a formula) X is -N(R8)-, -C(R9) (R10)-, -CO-, or -CO-N (R8). - (among a formula) R8 shows a hydrogen atom, -SO two R16 (R16 shows a low-grade alkyl group or an aryl group), or a low-grade alkyl group. The low-grade alkyl group concerned is a lower alkoxy group, an aryloxy group, and -N (R11) (R12) (R11 and R12). It becomes together with the nitrogen atom which shows a hydrogen atom or a low-grade alkyl group, or they combine independently, respectively. 5 which may contain at least one hetero atom chosen from the group which furthermore consists of a nitrogen atom, an oxygen atom, and a sulfur atom - 7 member heterocycle may be formed. You may permute by the substituent chosen from the group which consists of a carboxy group, a low-grade cycloalkyl radical, and an aryl group that may be permuted. R9 and R10 Independently, it may become together with the carbon atom which shows a hydrogen atom or a low-grade alkyl group, or they combine, and low-grade cycloalkane may be formed, respectively. It is shown. or 5 which may contain at least one hetero atom chosen from the group which becomes together with the carbon atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle -- you may form -- m -- the integer of 0 or 1 thru/or 3 -- being shown -- the radical expressed -- being shown --;B -- an aryl group or an aromatic series heterocycle radical -- being shown --;R5 -- (1) hydrogen atom -- (2) A halogen atom, (3) low-grade alkyl group, (4) lower alkoxy groups, (5) A cyano group, (6) nitro groups, (7) low-grade halo alkyl group, or (8)-S(O) r-R17 (R17 shows a low-grade alkyl group or an aryl group) r -- 0, 1, or 2 -- being shown -- being shown --;R6 -(Y) s1-(A2) s-Z (s1 and s among a formula) 0 or 1 is shown independently, respectively. Y -O-, -S(O) t-, - N(R13)-, -N(R14)-CO-, -N(R14)-SO2-, - SO2-N(R14)-, -C(R18) (R19)-, or -CO - (among a formula) t -- 0, 1, or 2 -- being shown -- R13 -- (1) hydrogen atom and (2) low-grade alkyl group (the low-grade alkyl group concerned

-- (a) low-grade cycloalkyl radical --) (b) You may permute by the substituent chosen from the group which consists of the aryl group which may be permuted, a heterocycle radical by which (c) permutation may be carried out, and a (d) hydroxyl group. (3) A low-grade alkenyl radical, (4) low-grade alkyl sulfonyl group, or (5) low-grade alkyl carbonyl group (the low-grade alkyl carbonyl group concerned may be permuted by the hydroxyl group or the lower alkoxy group) is shown. R14 shows a hydrogen atom or a low-grade alkyl group. R18 and R19 Independently, it may become together with the carbon atom which shows a hydrogen atom or a low-grade alkyl group, or they combine, and low-grade cycloalkane may be formed, respectively. It is shown. or 5 which may contain at least one hetero atom chosen from the group which becomes together with the carbon atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle -- you may form -- A2 shows the low-grade alkylene group which may be permuted by the low-grade cycloalkyl radical. Z (1) low-grade cycloalkyl radical (the low-grade cycloalkyl radical concerned may be permuted by the phenyl group which may be permuted), (2) -- an aryl group (the heterocycle radical which may be permuted by the substituent chosen from the group which the aryl group concerned becomes from (a) low-grade alkyl group and a low-grade alkyl carbonyl group --) (b) The low-grade cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and a low-grade alkyl group, (c) A carboxy group, (d) halogen atom, the (e) alkyl group, (f) low-grade halo alkyl group, (g) A low-grade alkylamino radical, (h) JI (low-grade alkyl) amino group, (i) You may permute by the substituent chosen from the group which consists of a low-grade alkylthio group and a (j) lower alkoxy group. (3) -- the aromatic series heterocycle radical which may be permuted, (4) indanyl radical, or (5) piperazinyl radical (the piperazinyl radical concerned -- the (a) phenyl group --) (b) Phenyl low-grade alkyl group, (c) -- it permutes by the substituent chosen from the group which consists of the benzoyl and (d) phenyl low-grade alkoxy carbonyl group which may be permuted by the halogen atom -- having -- **** -- the azole compound shown by] which shows the radical expressed, or its prodrug -- Or the salt which can be permitted on those remedies.
[Claim 2] In a general formula [I], W shows a sulfur atom or an oxygen atom, and;R is (1)-COOR7 (among a formula). R7 is (2)-X1-A1-COOR7 (among a formula) which shows a hydrogen atom or C1-4 alkyl group. X1 is -O-, -N(R15)-, or -S(O) p. - (R15 shows a hydrogen atom or C1-4 alkyl group among a formula) (3) tetrazolyl groups are shown. p -- 0, 1, or 2 -- being shown -- independently R1, R2, R3, and R4, respectively, or it is shown, A1 shows C1-4 alkylene group and R7 shows a hydrogen atom or C1-4 alkyl group (1) A hydrogen atom, (2) halogen atom, (3) hydroxyl groups, the C3-7 cycloalkyl C1-4 alkyloxy radical by which (4) permutations may be carried out, (5) The aralkyloxy radical which may be permuted, (6) cyano groups, (7) nitro groups, (8) C1-4 alkyl group, a (9) C1-4 halo alkyl group, (10) C1-4 alkoxy group, or a (11) C1-4 haloalkoxy radical is shown, and;A is -(CH2) m-X. - (among a formula) X is -N(R8)-, -C(R9) (R10)-, -CO-, or -CO-N (R8). - (among a formula) R8 shows a hydrogen atom, - SO two R16 (R16 shows C1-6 alkyl group or an aryl group), or C1-6 alkyl group. The C1-6 alkyl group concerned is C1-4 alkoxy group, an aryloxy group, and -N (R11) (R12) (R11 and R12). Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or 5 which may contain at least one hetero atom chosen from the group which becomes together with the nitrogen atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle may be formed. You may permute by the substituent chosen from the group which consists of a carboxy group, a C3-7 cycloalkyl radical, and an aryl group that may be permuted. R9 and R10 Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or it may become together with the carbon atom which they combine, and three to C7 cycloalkane may be formed. It is shown. or 5 which may contain at least one hetero atom chosen from the group which becomes together with the carbon atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle -- you may form -- m -- the integer of 0 or 1 thru/or 3 -- being shown -- the radical expressed -- being shown --;B -- an aryl group or an aromatic series heterocycle radical -- being shown --;R5 -- (1) hydrogen atom -- (2) A halogen atom, (3) C1-4 alkyl group, (4) C1-4 alkoxy group, (5) A cyano group, (6) nitro groups, a (7) C1-4 halo alkyl group, or (8)-S (O) r-R17 (R17 shows C1-6 alkyl group or an aryl group) r -- 0, 1, or 2 -- being shown -- being shown --

;R6 -(Y) s1-(A2) s-Z (s1 and s among a formula) 0 or 1 is shown independently, respectively. Y -O-, -S (O) t-, - N(R13)-, -N(R14)-CO-, -N(R14)-SO2-, - SO2-N(R14)-, -C(R18) (R19)-, or -CO - (among a formula) t -- 0, 1, or 2 -- being shown -- R13 -- (1) hydrogen atom and (2) C1-4 alkyl group (the C1-4 alkyl group concerned -- a (a) C3-7 cycloalkyl radical --) (b) You may permute by the substituent chosen from the group which consists of the aryl group which may be permuted, a heterocycle radical by which (c) permutation may be carried out, and a (d) hydroxyl group. (3) A C2-4 alkenyl radical, a (4) C1-4 alkyl sulfonyl group, or a (5) C1-4 alkyl carbonyl group (the C1-4 alkyl carbonyl group concerned may be permuted by the hydroxyl group or the C1-4 alkoxy group) is shown. R14 shows a hydrogen atom or C1-4 alkyl group. R18 and R19 Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or it may become together with the carbon atom which they combine, and three to C7 cycloalkane may be formed. It is shown. or 5 which may contain at least one hetero atom chosen from the group which becomes together with the carbon atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle -- you may form -- A2 shows the C1-4 alkylene group which may be permuted by the C3-7 cycloalkyl radical. Z A (1) C3-7 cycloalkyl radical (the C3-7 cycloalkyl radical concerned may be permuted by the phenyl group which may be permuted by the halogen atom), (2) -- an aryl group (the heterocycle radical which may be permuted by the substituent chosen from the group which the aryl group concerned becomes from (a) C1-4 alkyl group and a C1-4 alkyl carbonyl group --) (b) The C3-7 cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (c) A carboxy group, (d) halogen atom, (e) C1-8 alkyl group, (f) A C1-4 halo alkyl group, a (g) C1-4 alkylamino radical, (h) You may permute by the substituent chosen from the group which consists of the JI (one to C4 alkyl) amino group, (i) C1-4 alkylthio group, and (j) C1-4 alkoxy group. (3) -- an aromatic series heterocycle radical (the heterocycle radical by which the aromatic series heterocycle radical concerned may be permuted by (a) C1-4 alkyl group --) (b) The aryl group which may be permuted by C1-6 alkyl group, (c) halogen atom, or the C1-4 halo alkyl group, (d) A halogen atom, a (e) C1-4 halo alkyl group, the (f) carboxy group, (g) You may permute by the substituent chosen from the group which consists of a C3-7 cycloalkyl radical and (h) C1-4 alkoxy group. (4) -- an indanyl radical or (5) piperazinyl radical (the piperazinyl radical concerned -- the (a) phenyl group --) (b) Phenyl C1-4 alkyl group, (c) -- it permutes by the substituent chosen from the group which consists of the benzoyl and the (d) phenyl C1-4 alkoxy carbonyl group which may be permuted by the halogen atom -- having -- **** -- the azole compound according to claim 1 in which the radical expressed is shown, or its prodrug -- Or the salt which can be permitted on those remedies.
[Claim 3] W is a sulfur atom or an oxygen atom, and R is (1)-COOR7 (among a formula). R7 is (2)-X1-A1-COOR7 (among a formula) which shows a hydrogen atom. (3) tetrazolyl groups are shown. Or X1 shows -O-, A1 shows C1-4 alkylene group and R7 shows a hydrogen atom, R1, R2, R3, and R4 Independently, respectively (1) hydrogen atom, (2) halogen atom, (3) hydroxyl groups, (4) The aralkyloxy radical by which the C3-7 cycloalkyl C1-4 alkyloxy radical which may be permuted, or (5) permutations may be carried out is shown, and;A is -(CH2) m-X. - (among a formula) X is -N(R8)-, -C (R9) (R10)-, or -CO. - (among a formula) R8 shows a hydrogen atom or C1-6 alkyl group, and the C1-6 alkyl group concerned is C1-4 alkoxy group, an aryloxy group, and -N (R11) (R12) (R11 and R12). Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or 5 which may contain at least one hetero atom chosen from the group which becomes together with the nitrogen atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle may be formed. You may permute by the substituent chosen from the group which consists of a carboxy group, a C3-7 cycloalkyl radical, and an aryl group that may be permuted. R9 and R10 Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or it may become together with the carbon atom which they combine, and three to C7 cycloalkane may be formed. It is shown. or 5 which may contain at least one hetero atom chosen from the group which becomes together with the carbon atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle -- you may form -- m -- the integer of 0 or 1 thru/or 3 -- being shown -- the radical expressed -- being shown --;B -- an aryl group or an aromatic

series heterocycle radical -- being shown --;R5 -- (1) hydrogen atom -- (2) A halogen atom, (3) C1-4 alkyl group, or (4) C1-4 alkoxy group is shown, and;R6 are -(Y) s1-(A2) s-Z (s1 and s among a formula). 0 or 1 is shown independently, respectively. Y -O-, -S(O) t-, - N(R13)-, -N(R14)-CO-, or -N (R14)-SO2 - (among a formula) t -- 0, 1, or 2 -- being shown -- R13 -- (1) hydrogen atom and (2) C1-4 alkyl group (the C1-4 alkyl group concerned -- a (a) C3-7 cycloalkyl radical --) (b) You may permute by the substituent chosen from the group which consists of the aryl group which may be permuted, a heterocycle radical by which (c) permutation may be carried out, and a (d) hydroxyl group. (3) A C2-4 alkenyl radical, a (4) C1-4 alkyl sulfonyl group, or a (5) C1-4 alkyl carbonyl group (the C1-4 alkyl carbonyl group concerned may be permuted by the hydroxyl group or the C1-4 alkoxy group) is shown. It is shown and A2 shows the C1-4 alkylene group which may be permuted by the C3-7 cycloalkyl radical. R14 -- a hydrogen atom or C1-4 alkyl group -- being shown -- Z A (1) C3-7 cycloalkyl radical (the C3-7 cycloalkyl radical concerned may be permuted by the phenyl group), (2) -- an aryl group (the heterocycle radical by which the aryl group concerned may be permuted by (a) C1-4 alkyl group or the C1-4 alkyl carbonyl group --) (b) The C3-7 cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (c) A carboxy group, (d) halogen atom, (e) C1-8 alkyl group, (f) A C1-4 halo alkyl group, a (g) C1-4 alkylamino radical, and (h) JI (one to C4 alkyl) amino group, (i) Even if it permutes by the substituent chosen from the group which consists of C1-4 alkylthio group and (j) C1-4 alkoxy group, it is good (3) aromatic-series heterocycle radical (the aromatic series heterocycle radical concerned). (a) You may permute by the substituent chosen from the group which consists of a phenyl group which may be permuted by the heterocycle radical, (b) C1-4 alkyl group and (c) halogen atom, or the C1-4 halo alkyl group. (4) -- an indanyl radical or (5) piperazinyl radical (the piperazinyl radical concerned -- the (a) phenyl group --) (b) -- it permutes by the substituent chosen from the group which consists of phenyl C1-4 alkyl group and a (c) phenyl C1-4 alkoxy carbonyl group -- you may have -- the salt which can be permitted on the azole compound according to claim 2 in which the radical expressed is shown, its prodrug, or those remedies.

[Claim 4] The azole compound according to claim 3 whose W is a sulfur atom and whose m is 0 or 1, its prodrug, or the salt which can be permitted on those remedies.

[Claim 5] A is -(CH2) m-X. - (the inside of a formula and X are -N(R8)- (R8 shows a hydrogen atom or C1-6 alkyl group among a formula)) The C1-6 alkyl group concerned is C1-4 alkoxy group, an aryloxy group, and -N (R11) (R12) (R11 and R12). Independently, respectively [whether a hydrogen atom or C1-4 alkyl group is shown and] Or 5 which may contain at least one hetero atom chosen from the group which becomes together with the nitrogen atom which they combine, and consists of a nitrogen atom, an oxygen atom, and a sulfur atom further - 7 member heterocycle may be formed. It is shown. it permutes by the substituent chosen from the group which consists of a carboxy group, a C3-7 cycloalkyl radical, and an aryl group that may be permuted -- having -- **** -- m -- 0 or 1 -- being shown -- the salt which can be permitted on the azole compound according to claim 4 in which the radical expressed is shown, its prodrug, or those remedies.

[Claim 6] The azole compound according to claim 5 whose R is -X1-A1-COOR7 (the inside of a formula and each notation are passages according to claim 3), its prodrug, or the salt which can be permitted on those remedies.

[Claim 7] The azole compound according to claim 5 whose R is -COOR7 (R7 shows a hydrogen atom among a formula), its prodrug, or the salt which can be permitted on those remedies.

[Claim 8] The azole compound according to claim 7 R1, R2, R3, and whose R4 are hydrogen atoms, its prodrug, or the salt which can be permitted on those remedies.

[Claim 9] The azole compound according to claim 8 whose B is a phenyl group, a thiazolyl radical, a pyridyl radical, a benzothiazolyl radical, a benzoimidazolyl radical, or a benzoxazolyl radical, its prodrug, or the salt which can be permitted on those remedies.

[Claim 10] The azole compound according to claim 9 whose B is a phenyl group, its prodrug, or the salt which can be permitted on those remedies.

[Claim 11] The azole compound according to claim 10 whose R5 is a hydrogen atom, its prodrug, or the

salt which can be permitted on those remedies.
[Claim 12] In R6 Z A (1) C3-7 cycloalkyl radical (the C3-7 cycloalkyl radical concerned may be permuted by the phenyl group), (2) -- an aryl group (the heterocycle radical by which the aryl group concerned may be permuted by (a) C1-4 alkyl group or the C1-4 alkyl carbonyl group --) (b) The C3-7 cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (c) A carboxy group, (d) halogen atom, (e) C1-8 alkyl group, (f) A C1-4 halo alkyl group, a (g) C1-4 alkylamino radical, (h) Or you may permute by the substituent chosen from the group which consists of the JI (one to C4 alkyl) amino group, (i) C1-4 alkylthio group, and (j) C1-4 alkoxy group, it is (3) aromatic-series heterocycle radical (the aromatic series heterocycle radical concerned). (a) -- it permutes by the substituent chosen from the group which consists of a phenyl group which may be permuted by the heterocycle radical, (b) C1-4 alkyl group and (c) halogen atom, or the C1-4 halo alkyl group -- having -- **** -- the shown azole compound according to claim 11 or its prodrug -- Or the salt which can be permitted on those remedies.
[Claim 13] The heterocycle radical by which Z may be permuted by (a) C1-4 alkyl group or the C1-4 alkyl carbonyl group, (b) The C3-7 cycloalkyl radical which may be permuted by the substituent chosen from the group which consists of a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (c) A carboxy group, (d) halogen atom, (e) C1-8 alkyl group, (f) A C1-4 halo alkyl group, a (g) C1-4 alkylamino radical, (h) The azole compound according to claim 12 in which the aryl group which may be permuted by the substituent chosen from the group which consists of the JI (one to C4 alkyl) amino group, (i) C1-4 alkylthio group, and (j) C1-4 alkoxy group is shown, or its prodrug, Or the salt which can be permitted on those remedies.
[Claim 14] The cyclohexyl radical or cyclopentylic group which may be permuted by the substituent chosen from the group which Z becomes from the (a) hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group, (b) -- the heterocycle radical (the heterocycle radical concerned -- a piperidinyl radical --) which may be permuted by C1-4 alkyl group or the C1-4 alkyl carbonyl group A mol HORINIRU radical, a piperazinyl radical, a tetrahydropyranyl group, The azole compound according to claim 13 which is the phenyl group permuted by the substituent chosen from the group which consists of (c) C1-8 alkyl group and it is chosen from the group which consists of a pyrrolidinyl radical and a pyrrolyl radical, its prodrug, or the salt which can be permitted on those remedies.
[Claim 15] The azole compound according to claim 14 in which the phenyl group permuted by the cyclohexyl radical which may be permuted by the substituent chosen from the group which Z becomes from a hydroxyl group, an oxo-radical, a halogen atom, and C1-4 alkyl group is shown, its prodrug, or the salt which can be permitted on those remedies.
[Claim 16] It sets to R6 and Y is -O-, -N(R13)-, or -N(R14)-CO. - (among a formula) R13 shows a hydrogen atom, C1-4 alkyl group, or a C2-4 alkenyl radical. The C1-4 alkyl group concerned A C3-7 cycloalkyl radical, the aryl group which may be permuted, You may permute by the substituent chosen from the group which consists of the heterocycle radical and hydroxyl group which may be permuted. R14 -- a hydrogen atom or C1-4 alkyl group -- being shown -- the salt which is shown and can be permitted on the azole compound according to claim 13 or 14 whose s1 is 1, its prodrug, or those remedies.
[Claim 17] The salt which can be permitted in R6 on the azole compound according to claim 16 whose A2 is a methylene group, its prodrug, or those remedies.
[Claim 18] The remedy constituent containing an azole compound according to claim 1 to 17, its prodrug or the salt that can be permitted on those remedies, and the support which can be permitted on a remedy.
[Claim 19] The remedy constituent for protein thyrosin phosphatase 1B inhibition containing an azole compound according to claim 1 to 17, its prodrug or the salt that can be permitted on those remedies, and the support which can be permitted on a remedy.
[Claim 20] The remedy constituent for a diabetes-mellitus therapy containing an azole compound according to claim 1 to 17, its prodrug or the salt that can be permitted on those remedies, and the support which can be permitted on a remedy.

[Claim 21] The remedy constituent for a hyperlipidemia therapy containing an azole compound according to claim 1 to 17, its prodrug or the salt that can be permitted on those remedies, and the support which can be permitted on a remedy.
[Claim 22] The remedy constituent according to claim 18 for concomitant use with other hyperlipidemia remedies.
[Claim 23] The remedy constituent according to claim 22 whose hyperlipidemia remedies are the drugs of a SUTACHIN system.
[Claim 24] The remedy constituent according to claim 23 chosen from the group which the drugs of a SUTACHIN system become from lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, and auction bus TACHIN.
[Claim 25] The remedy constituent according to claim 18 for concomitant use with other diabetic medicine.
[Claim 26] The remedy constituent according to claim 25 for concomitant use with the diabetic medicine chosen from the group which consists of the insulin secretagogue, sulfonyl urea medicine, sulfonamide medicine, BIGUANAIDO medicine, alpha GURUKO cytase inhibitor, insulin preparation, and insulin resistance improvement medicine.
[Claim 27] The remedy constituent according to claim 26 chosen from the group which diabetic medicine becomes from nateglinide, glimepiride, glibenclamide, gliclazide, acetohexamide, tolbutamide, glyclopyramide, tolazamide, glybuzole, metformin hydrochloride, buformin hydrochloride, voglibose, acarbose, an insulin, and pioglitazone hydrochloride.
[Claim 28] The remedy constituent according to claim 20 for concomitant use with other hyperlipidemia remedies.
[Claim 29] The remedy constituent according to claim 28 whose hyperlipidemia remedies are the drugs of a SUTACHIN system.
[Claim 30] The remedy constituent according to claim 29 chosen from the group which the drugs of a SUTACHIN system become from lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, and auction bus TACHIN.
[Claim 31] The remedy constituent according to claim 20 for concomitant use with other diabetic medicine.
[Claim 32] The remedy constituent according to claim 31 for concomitant use with the diabetic medicine chosen from the group which consists of the insulin secretagogue, sulfonyl urea medicine, sulfonamide medicine, BIGUANAIDO medicine, alpha GURUKO cytase inhibitor, insulin preparation, and insulin resistance improvement medicine.
[Claim 33] The remedy constituent according to claim 32 chosen from the group which diabetic medicine becomes from nateglinide, glimepiride, glibenclamide, gliclazide, acetohexamide, tolbutamide, glyclopyramide, tolazamide, glybuzole, metformin hydrochloride, buformin hydrochloride, voglibose, acarbose, an insulin, and pioglitazone hydrochloride.
[Claim 34] The remedy constituent according to claim 21 for concomitant use with other hyperlipidemia remedies.
[Claim 35] The remedy constituent according to claim 34 whose hyperlipidemia remedies are the drugs of a SUTACHIN system.
[Claim 36] The remedy constituent according to claim 35 chosen from the group which the drugs of a SUTACHIN system become from lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, and auction bus TACHIN.
[Claim 37] The remedy constituent according to claim 21 for concomitant use with other diabetic medicine.
[Claim 38] The remedy constituent according to claim 37 for concomitant use with the diabetic medicine chosen from the group which consists of the insulin secretagogue, sulfonyl urea medicine, sulfonamide medicine, BIGUANAIDO medicine, alpha GURUKO cytase inhibitor, insulin preparation, and insulin resistance improvement medicine.
[Claim 39] The remedy constituent according to claim 38 chosen from the group which diabetic

medicine becomes from nateglinide, glimepiride, glibenclamide, gliclazide, acetohexamide, tolbutamide, glyclopyramide, tolazamide, glybuzole, metformin hydrochloride, buformin hydrochloride, voglibose, acarbose, an insulin, and pioglitazone hydrochloride.

[Translation done.]